FAST TRACK: PHASE I SEGMENT SPECIFIC AIMS

The primary objective of this fast track STTR proposal is to create and evaluate a multimedia intervention program for women with cancer-related sexual dysfunction. *Tendrils: A Sexual Renewal Program for Women Surviving Cancer* will provide educational information and instructions for cognitive-behavioral interventions to prevent or alleviate cancer-related sexual problems. *Tendrils* will be designed: 1) to answer women's questions about cancer-related sexual dysfunction; 2) to offer self-help strategies to overcome problems; 3) to encourage women to seek medical help when appropriate; and 4) possibly to serve as the nucleus of a brief, professional counseling program, along with a therapist manual. Its content will be comprehensive and medically accurate, using tasteful animations rather than live actors to illustrate any direct genital anatomy or sexual options. Situations that should trigger consultation with a physician will be highlighted. Despite the many different cancer sites and treatments for women, sexual dysfunction after cancer tends to divide into several common patterns, particularly loss of desire, genital pain, and concerns about being attractive and lovable to a partner. *Tendrils* will be relevant to a broad spectrum of women, from newly diagnosed to long-term survivors, with sections for women with specific cancer sites or with advanced disease. A section for partners will also be included. Designed to appeal to women of differing ethnicity, literacy level, and sexual orientation, *Tendrils* will present material on a variety of religious and cultural attitudes about female sexuality. The software used to construct it will allow women to interact with the material in a variety of formats, including printed out pages, computer animations, and digital video or audio files that can be used on a computer or downloaded to a personal digital assistant or media player. Video vignettes portrayed by actors will illustrate problems and solutions. Five cancer survivors of varying age, ethnicity, and sexual orientation will host the program, sharing their experiences. Cancervive, Inc. will create these videos, which will be viewable as whole stories or in shorter segments linked to relevant content. **Although the plan for Phase I and II does not include translation to Spanish, mainly because of added expense to the budget, translation will be accomplished as part of commercialization.**

Table 1 presents tasks, milestones, and a timeline. Our previous research has demonstrated that

Table 1. Specific Tasks and Milestones of Phase I

Task	Months	Responsibility	Milestone
Write the actual text for *Tendrils*, including education, cognitive-behavioral exercise instructions, forms to record homework progress, etc.	1-4	UTMDACC primary AXIS editing and proofing	All text complete, including concepts for animations. Two animations storyboarded to use as examples for reviewers. Two scripts for vignettes written to use as examples.
Write the scripts for two vignettes to be videotaped with actors, illustrating clinical situations and techniques to serve as samples for reviewers	1-4	UTMDACC primary AXIS editing and proofing	
Create storyboards for two animations to illustrate anatomy, sexual response, etc. to serve as samples for reviewers	1-4	UTMDACC content and captions, AXIS storyboards	
Get feedback from panel of expert professionals and advocates on text, sample vignettes and sample animations. Review by Susan Nessim Keeney, consultant.	5-6	AXIS primary, UTMDACC and Cancervive secondary	All text and sample animations and scripts reviewed by panel of expert professionals and advocates, and by patient focus groups, and rated as easy to understand, easy to navigate, and useful by ≥ 75% (criterion score of ≤ 22 on 11-item evaluation rating form).
Conduct focus groups of female cancer survivors to evaluate feasibility of content: Age 18-35; 36-55; ≥56	5-6	UTMDACC	

many cancer survivors with sexual problems can improve sexual function and satisfaction via relatively brief, psychoeducational sexual counseling interventions. We are confident that a multimedia intervention is

feasible, and at the very least will fill a gap in patient education and encourage appropriate medical care. The **specific aims for the 6 months of Phase I are: 1) to create a first draft of the content of *Tendrils*, including informational text, cognitive-behavioral exercises, storyboards of at least 2 sample animations, and scripts for at least 2 sample video vignettes (to be filmed in Phase II with actors).** Much of the content of the intervention can be modified or expanded from our previous educational materials and counseling programs. **2) To demonstrate feasibility by showing that the prototype is easy to understand, easy to navigate, and relevant to women's concerns.** All text, and at least two sample animations and video vignettes in prototype form (text, storyboards, and scripts) will be presented on a website, and rated a panel of expert professionals and cancer advocates, as well as by focus groups of female survivors. Our criterion for feasibility is that at least 75% of raters score *Tendrils* as easy to understand, easy to navigate, and relevant to female sexual dysfunction after cancer. Panel members will also review the content for medical accuracy and give other feedback relevant to their area of expertise.

We will begin Phase II ready to revise content, create the rest of the animations and video scripts, cast and videotape several women survivors' stories, and construct a prototype product. Susan Nessim Keeney of Cancervive will serve as a consultant in the role of "site administrator" as suggested by the National Cancer Institute's Multimedia Technology Health Communication's SBIR/STTR Program, giving us advice on shaping *Tendrils* for later marketing directly to cancer survivors or to oncology health professionals.

FAST TRACK PHASE II SEGMENT: SPECIFIC AIMS

Table 2 presents the tasks, milestones, and a timeline for the 3 years of Phase II.

Table 2. Specific Tasks and Milestones of Phase II

Task	Months	Responsibility	Milestone
Revise and complete text using feedback from phase I	1-3	UTMDACC primary AXIS editing and proofing	
Search for 5 survivors to tell their stories of sexual rehabilitation	1-3	Cancervive primary, UTMDACC and AXIS consulting	
Create visual prototype of website with graphics and text, scheme for navigation	3-6	AXIS primary, UTMDACC editing	
Create concepts for all animations and create them in robust media	3-6	AXIS primary, UTMDACC editing	All text and artwork ready for creation of multimedia prototype
Write scripts for video vignettes	4-6	UTMDACC primary AXIS editing and proofing	
Program features of the website, such as the ability to record usage by each participant (time spent on each page, number of log-ins, number of print-outs or downloads, etc.)	1-8	AXIS primary, UTMDACC consultation on required features	
Create outline of story for each of the survivors	4-6	Cancervive subcontract, UTMDACC and AXIS consulting	
Videotape the survivor interviews	7-8	Cancervive subcontract, UTMDACC and AXIS consulting	
Videotape the scripted vignettes with actors, illustrating clinical situations and techniques	7-8	AXIS primary, UTMDACC consults on taping and editing	Prototype of *Tendrils* complete and ready for review.

Get feedback from panel of expert professionals and advocates on prototype of *Tendrils*	8-9	AXIS	
Test usability and content of *Tendrils* at the National Cancer Institute's Technology Center	8-9	AXIS	Prototype reviewed by panel and NCI Technology Center
Create therapist manual for a 3-session supplemental counseling intervention by master's-level counselors, based on *Tendrils*	6-12	UTMDACC	
Revise text and scripts as needed	10-12	UTMDACC primary AXIS editing and proofing	
Train counselor(s) to do the intervention	9-12	UTMDACC	
Create database for online entry of questionnaires	10-12	UTMDACC primary, AXIS consulting	
Install website on UTMDACC server	10-12	UTMDACC primary, AXIS consulting	Revised version of *Tendrils* ready for randomized trial. Therapist manual and training complete.
Recruit 240 survivors of breast or gynecologic cancer and conduct randomized trial comparing *Tendrils* on self-help basis vs. with brief counseling	12-24	UTMDACC	
Collect follow-up questionnaires at 3- and 6-months	15-30	UTMDACC	
Conduct statistical analyses, write reports, submit journal article	31-36	UTMDACC	Complete randomized trial of *Tendrils* as self-help vs. with counseling, also examine relationships between age, education, and extent and of media use and change in outcome measures; primarily improved sexual function and satisfaction; secondarily better quality of life and less emotional distress
Use information on media preferences and outcomes from trial to create final version of *Tendrils* including translation into Spanish	31-36	AXIS primary, UTMDACC secondary	
Use information from randomized trial to finalize commercialization plan	31-36	AXIS	Finalize commercialization plan and prepare to implement it

As we develop *Tendrils* in Phase II, we hope to demonstrate that in addition to providing a much-needed educational resource for cancer survivors, *Tendrils* will produce significant improvement in women's sexual function and satisfaction (see Background and Significance section). **The SPECIFIC AIMS of the 3 years of Phase II are 1) to use the feedback from Phase I to complete a multimedia prototype of *Tendrils* that is easy to use, easy to navigate, relevant to survivors' sexual concerns, and medically accurate; 2) to test its efficacy in a randomized trial comparing its use on a self-help basis vs. in the context of counseling; and 3) to use the results of the randomized trial to make final revisions before commercialization and to target marketing to the format that is most efficacious, which may differ for specific demographic groups of cancer survivors.**

Our PRIMARY HYPOTHESIS for the randomized trial is that *Tendrils* will produce significant improvements in sexual function and satisfaction whether used on a self-help basis or with brief counseling, but that the group receiving counseling will improve significantly more than the self-help group. Secondary hypotheses are that the incremental improvement with counseling will be greater for less educated women and older women. Time spent using *Tendrils* will be examined as a potential mediating factor in outcome.

Potential for Technological Innovation and Commercial Application. *Tendrils* is important because it addresses a highly prevalent problem for female cancer survivors that has rarely been tackled in intervention research. By creating a multimedia tool that can be used either on a self-help basis or as part of a manualized, brief counseling intervention by oncology nurses or social workers, our product potentially overcomes the following barriers to successful sexual rehabilitation for women after cancer:

- Existing patient education materials only explore basic issues and are formatted for well-educated women who read brochures or self-help books.
- Few health care professionals are trained to deliver sexual counseling for cancer-related dysfunction.
- Seeking help from a mental health professional for a sexual problem is still stigmatized.
- Insurance coverage is poor for traditional sexual counseling from a mental health professional.
- Women often are unsuccessful in finding a medical specialist who can treat physical causes of sexual dysfunction.

BACKGROUND AND SIGNIFICANCE

The Problem: Female Sexual Dysfunction Remains Highly Prevalent for Years after Cancer Treatment. Sexual problems related to cancer treatment affect approximately half of women who are survivors of breast or pelvic cancer and a smaller, but still significant, proportion of women treated for hematological or other malignancies. The total number of female cancer survivors in the United States (US) in 2004 was estimated to be about 5.6 million. Pelvic and breast cancers comprise over two-thirds of the disease sites for these women.[1] In 2005 another 397,220 women were expected to receive new diagnoses of pelvic or breast tumors.[2] Thus a conservative estimate is that 3 million cancer survivors in the US suffer from sexual dysfunction. Not only is sexual dysfunction very common after cancer, but it is typically pervasive, diminishing a woman's sexual desire and pleasure. Sexual dysfunction also persists long after cancer treatment, in contrast to other sources of psychosocial distress.[3] The types of sexual problems that women experience after cancer have been well-described. Their causes are known and brief counseling is often effective at resolving them.[3-5] Yet, few researchers have tried to create or evaluate programs of sexual rehabilitation.

The Opportunity: Limited Availability of Information and Treatment for Cancer-Related Sexual Problems. In its 2003-2004 report, Living Beyond Cancer, the President's Cancer Panel made this recommendation: "Health care providers should not assume that older cancer survivors and their partners are uninterested in sexuality and intimacy. Survivors should be asked directly if they have concerns or are experiencing problems in this area and should receive appropriate referrals to address such issues."[6]

However, women of all ages treated in the United States and other developed countries still tend to receive little or no information on cancer-related sexual dysfunction.[7] A survey of the patient education departments of comprehensive cancer centers in 2002 revealed that only 14% offered counseling on sexuality.[8] In a cohort of 166 well-educated women diagnosed in the Northeast with premenopausal breast cancer, only 68% recalled being informed about premature menopause by one of their physicians, let alone having a discussion directly about sexual function.[9] Interviews of 39 lesbian or bisexual women treated for breast cancer revealed that health care providers never inquired about sexual orientation, although 72% of women initiated disclosure with their oncologists.[10] Knowing a woman's sexual orientation is important for her health care providers not only for sexual counseling, but because lesbian women are at heightened risk for breast cancer, as well as cardiovascular disease and depression.[11] The situation in other English-speaking developed countries is quite similar. In England, a survey of members of multidisciplinary oncology teams showed that the clinical nurse specialist was often the only one to discuss sexual issues.[12] In a study focused on health care providers for women with ovarian cancer, the same researchers found that only 25% of oncologists and 20% of nurses discussed sexuality with the patients. A major reason for failing to bring up the topic was lack of knowledge or resources for support and referral.[13] A survey of radiation oncology clinics in Australia found that there was not even consistency on prevalence or type of advice given to women on using vaginal dilators after their treatment,[14] despite consensus that dilation may prevent vaginal stenosis.[15]

The Solution: *Tendrils* as a Multimedia Self-Help Intervention or as Part of a Counseling Package. Providing information about overcoming cancer-related sexual dysfunction directly to women during and after their cancer treatment circumvents the problem of health care providers too embarrassed, busy, or untutored to offer help. A self-help, multimedia tool can also be marketed at a very affordable price and can utilize audio, video, and animation media that appeals both to more educated and low literacy audiences. The National Cancer Institute's (NCI) Multimedia Technology Health Communication SBIR/STTR Grant Program includes in its list of topics for 2006: "Programs to educate both physicians and patients about reproductive health after cancer" including provision of "needed information to cancer patients and their family members." Suggested products include a CD-ROM, web site, or wireless technologies.

Counseling by a professional may enhance the efficacy of such an intervention beyond its use as a self-help modality, however, particularly for women who are older or less well-educated. Even if more cancer centers or oncology clinics offered sexual counseling, barriers to effective sexual rehabilitation include the stigmatization of psychological treatment in our culture, especially for women from ethnic minority cultures,[16] and the poorer quality of health care services for underserved patients, even under Medicare.[17] Another hurdle is the lack of mental health practitioners well-versed in treating both sexual dysfunction and psychosocial problems after cancer. Furthermore, most private insurers do not cover

psychological treatment if sexual dysfunction diagnoses are used. Even insurers willing to reimburse such services often restrict women to consulting a small panel of providers, further decreasing the likelihood of finding someone with dual expertise. For our randomized trial, we will create a therapist manual for the *Tendrils* program designed for use by oncology nurses or social workers who are master's-degree prepared and have some counseling background. We will see whether adding an affordable and practical number of counseling sessions (i.e. three), enhances the efficacy of the program for some or all women.

Rationale for Phase I Aim 1: Creating a Comprehensive Intervention Based on Current Knowledge of Cancer-Related Sexual Dysfunction in Women. Cancer and its treatments contribute to female sexual dysfunction in many different ways, since each cancer site, and its treatment options, is unique. Cancer treatment may damage the hormonal, neurological, and vascular systems involved in the sexual response, or may entail removing parts of the genital or pelvic reproductive system. Psychological factors in cancer-related sexual problems include disruption of body image, exacerbation of relationship stress, stigmatization, and negative beliefs about sex and cancer. The physiological damage to sexual function is often profound, however, so that psychological factors do not directly determine the sexual dysfunction, but rather contribute to a woman's distress levels, whether or not she resumes sexual activity, or whether she seeks medical help. When a cancer survivor is in a relationship, both partners' sexual attitudes influence the outcome of sexual rehabilitation. Psychological factors may explain why some women are more resilient under difficult circumstances. For example, what distinguishes the 50% of women who stay sexually functional despite prophylactic oophorectomy with no subsequent hormonal replacement? [18]

Typical female dysfunctions after cancer include loss of desire for sex and difficulty feeling arousal and pleasure. Difficulty achieving orgasm is less common, and often secondary to having sex with little desire or arousal. Risk factors for sexual dysfunction include surgery that removes tissue from the vulva or vagina[19] or radiation that damages the vagina's ability to expand and lubricate with sexual arousal.[3] Despite the focus of many studies on body image, breast conservation (lumpectomy and radiation) or reconstruction does not produce better sexual outcomes than mastectomy alone, whether measured in terms of frequency of sex, overall sexual satisfaction, or rates of sexual problems.[20-25]

Table 3 provides an overview of sexual problems associated with particular types of cancer, their prevalence, and causes. In women with breast cancer, as well as other malignancies, cancer treatments causing sudden ovarian failure in pre-menopausal women are the most likely to cause sexual dysfunction.[26] Whether both ovaries are removed surgically, are damaged beyond recovery by chemotherapy, or are within the target area of radiation therapy, ovarian failure can result in severe problems with vaginal dryness and pain during sexual activity. Women over age 35 are particularly likely to have permanent ovarian failure after more moderate doses of chemotherapy or radiation, whereas very young women may recover their menstrual cycles (although they are at risk to reach an early, permanent menopause).

Table 3. Female Sexual Dysfunction and Cancer

	Cancer Site		
	Breast	**Pelvic, vaginal, and vulvar**	**Hematologic cancers, sarcomas, and others**
Prevalence of sexual problems after treatment	• About 50%, dysfunctions tend to be global and persistent[20,21,27]	• 6% to 85% depending on cancer treatment; dysfunctions tend to be global and persistent [28-31]	• 25%-80%, mainly low desire; Risk factors: ovarian failure, bone marrow transplant (BMT)[32-35]
Significantly more than in peers without cancer?	• Similar to peers except significantly more if diagnosed before menopause with consequent ovarian failure[26,36,37]	• Significantly more in mixed group of mixed gynecologic cancer patients,[28] cervix cancer survivors,[38] or women with ovarian cancer[39] • Cervical cancer: Only in women treated with radiation therapy; if radical hysterectomy alone, resemble healthy peers[40-44]	• Unclear, few comparison studies have been done

Physiological factors in sexual dysfunction	• Breast conservation or reconstruction are not superior to mastectomy alone in preserving sexual function, frequency, or satisfaction[20-25] Sexual problems after prophylactic mastectomy in 20% to 70% [45-47] • Sexual problems mainly after treatments producing ovarian failure with loss of estrogen: vaginal atrophy; Low androgens: Less desire and subjective pleasure, i.e. chemotherapy[20,21,24,26,35,48,49] or prophylactic oophorectomy;[18,50] • Tamoxifen does not reduce sexual desire, may increase vaginal lubrication[21,24,49,51-53] • Raloxifene does not appear to cause sexual problems, studies thus far not in breast cancer survivors[54,55] • Aromatase inhibitors cause worse vaginal dryness and atrophy than tamoxifen[56] • Rates of menopausal vaginal atrophy may not unusual, but ore difficult to treat without estrogen replacement • Medication effects (opiate pain medication, psychotropic medication, anti-emetic medication) may blunt sexual desire or make it difficult to reach orgasm[57,58] • Loss of erotic breast sensation after mastectomy, not restored by breast reconstruction[24]	• Major factor: Ovarian failure caused by chemotherapy, pelvic radiotherapy, or bilateral oophorectomy; Loss of estrogen leads to vaginal dryness, atrophy, and pain with sexual activity; Loss of androgens may lessen desire and subjective pleasure from touch • Damage from radiotherapy to vagina progresses for years after treatment; Acute phase, vaginal walls can scar shut or develop radiation ulcers; Eventually reduced vaginal caliber and depth, especially at top of vagina, reduced lubrication with sexual arousal[59] • Temporary vaginal inflammation from direct effects of chemotherapy can cause pain during sexual activity[60] • Radical hysterectomy removes upper third to half of the vagina, but reduced depth not major problem for most women; Combined surgery and radiation therapy may be worse than either alone[41-44,61] • Loss of cervix does not decrease ability to feel pleasure with intercourse or achieve orgasm, as seen in studies of hysterectomy for benign disease or for cancer[62,63] • Pain with intercourse from reduced vaginal depth or caliber after radical cystectomy[64,65] • Using bladder reconstruction to modify radical cystectomy also leaves the anterior vaginal wall intact, and women report far less sexual dysfunction[66,67] • Loss of posterior vaginal cushioning with abdominoperineal resection causes pain during intercourse; Fewer problems after sphincter-saving surgery[31,68,69] • May need to cope with urinary ostomy, ileostomy, or colostomy; Newer surgical techniques that avoid ostomies may have sexual advantage[67-70] • Loss of clitoris and/or inner labia in radical vulvectomy: Decreased erotic pleasure or orgasm; Entrance to vagina may be narrowed by scarring; Pelvic lymph node surgery causes disfiguring leg lymphedema[71,72] • Estrogen replacement not as effective in reversing changes in	• Ovarian failure from chemotherapy, abdominal radiotherapy, total body irradiation before bone marrow transplant, or cranial irradiation; Loss of estrogen: vaginal dryness, atrophy, and pain; Loss of androgens may lessen desire and subjective pleasure[34,73,76] • Chemotherapy that spares fertility may not spare sexual function[33] • Graft- vs. host disease (immune reaction) after BMT: Extensive vaginal shortening and/or tight bands of scar tissue in 20% of women[77] • Chronic fatigue or depressed mood may contribute to low desire for sex • Medication (opiate pain medication, psychotropic medication, anti-emetic medication, steroids) may blunt sexual desire or interfere with orgasm[57,58] • May need to cope with surgical scars or limb amputation;Unclear that limb-sparing is superior to amputation in terms of sexual activity or satisfaction[78,79]

		irradiated vagina[73] • Sensory nerves important for orgasm in clitoris and vagina rarely damaged in pelvic cancer treatment[74] • Lack of erotic sensitivity in reconstructed vagina[75] • Deep pain during sex triggered by adhesions, scar tissue, or remaining ovary adhering to vaginal cuff • Medication effects (opiate pain medication, psychotropic medication, anti-emetic medication, steroids) may blunt sexual desire or interfere with orgasm[57,58]	
Psychological factors in sexual dysfunction	• Anxiety about attractiveness, breast appearance, weight gain; Women more invested in looks may be buffered against this distress[80] • Anxiety about partner's reaction to infertility, grief over own loss,[81] Loss of pleasure from breast caressing[24,47] • Distracting thoughts about cancer during sex interfere with desire and mental arousal; Often triggered by caressing of the breast area[24] • Anxiety about recurrence or familial breast cancer may contribute to loss of sexual desire[46-47,50] • A new relationship after cancer is positive factor[21] • Sexual abuse in past may interfere with post-cancer sexuality[82]	• Anxiety about attractiveness; For vulvar cancer, anxiety about appearance of genitals[83] • Anxiety about partner's reaction to infertility and grief over the loss[81] • Stigma of having cancer associated with a sexually-transmitted virus (cervical or vulvar cancer[84] • Negative self-image as sexual person [85,86] • Limited vulvar surgery may preserve sexual pleasure, but overall sexual satisfaction tied more to quality of woman's relationship than to amount of tissue spared[72] • History of childhood sexual abuse may interfere with emotional coping with impact of cervical cancer on sexuality[87]	• Anxiety about diminished attractiveness may interfere with dating or sexual initiation • Anxiety about partner's reaction to infertility and grief over the loss[81]
Common types of sexual problems	• Low desire for sex • Vaginal dryness • Pain with vulvar caressing and/or vaginal penetration • Post-coital bleeding	• Low desire for sex • Vaginal dryness • Pain with vulvar caressing and/or vaginal penetration • Post-coital bleeding	• Low desire for sex • Vaginal dryness • Pain with vulvar caressing and/or vaginal penetration

It is crucial to have a basic understanding of female sexual dysfunction in women unselected for health. When women in the United States (US) are surveyed about their sex lives, they report high rates of sexual dysfunction.[88,89] As many as 40% perceive themselves as lacking desire for sex, prompting many clinicians and researchers to rethink whether our model of spontaneous, hormone-driven sexual desire

applies well to females.[90] Women's ability to get sexually interested and aroused appears relationship- and context-driven. Sexual problems are more common in women with less education, in conflicted relationships, and/or belonging to an ethnic group or subculture that does not value sexual pleasure for females.[88,89,91] In contrast to male sexual dysfunction, which increases with age and ill health, women have fewer sexual problems with aging, except for vaginal dryness which is linked directly to estrogen deprivation.[88,91] In fact, women's ability to feel pleasure and reach orgasm has a large learned component, so that young women in casual relationships have higher rates of problems than older, married women.[88] Older women frequently are sexually inactive because they have no partner, however.[91]In the US and other English-speaking countries, only about 20% of women with sexual dysfunction seek medical help.[91,92] In a very large international survey, about half of women felt physicians should proactively inquire about sexual problems, yet only 10% had been asked about sex by a physician in the past year. [92] Even in a cohort of well-educated US women who completed an internet survey, only 40% consulted a health professional for their sexual problem.[93] In that group, less than half felt the physician was interested in hearing about the problem and only 14% received some kind of treatment plan. Forty-two percent consulted gynecologists about the problem and 24% saw a general practitioner. Given the added time pressures in a busy oncology clinic, women cancer survivors are unlikely to get better care for their sexual problems. In fact, as discussed in the introduction, few get the help they need.

Rationale for Phase II Aims 2 and 3. Comparing the Intervention in Self-Help vs. Counseling-Enhanced Formats and Marketing According to Results. Innovative treatments are needed to prevent or remediate cancer-related sexual dysfunction. A very few sexual counseling studies were published in the 1980s. A group intervention was superior to usual care in promoting a return to sexual activity after gynecologic cancer,[94] and a structured group had a positive impact on the sexuality of women recently treated with mastectomy.[95] Schover and colleagues published a retrospective review of sex therapy consultations over 4 years in a major cancer center.[4] Out of 384 individuals or couples, 73% were seen only once or twice. Of the index patients seen, 308 were men and 76 were women, who typically had a combination of loss of desire and vaginal dryness/dyspareunia. Follow-up data on outcome were available for only 118 cases of both genders. The therapist rating of improvement was "somewhat to much better" for 63% of this group. Factors correlated with better outcome included having more sessions, younger age, absence of depression, and absence of marital conflict.

Since the 1980's, only one published, randomized trial has examined the efficacy of a counseling intervention for post-cancer sexual dysfunction.[5] Seventy-six postmenopausal breast cancer survivors who had at least one severe problem of hot flashes, vaginal dryness, or urinary stress incontinence were randomized to usual care or to a special session with a nurse practitioner. The nurse assessed symptoms and applied treatment algorithms such as prescribing medication or advising on the use of vaginal lubricants. Telephone follow-up calls were included. All three target symptoms improved in the treated group compared to the usual care group. Thus, education and brief counseling can remediate many problems.

Loss of desire for sex is one of the most common and complex problems after cancer treatment. Risk factors include lingering post-treatment fatigue, pain, or nausea; distracting cognitions about feeling unattractive or stigmatized after cancer; medication side effects; mild depression; and relationship conflict exacerbated by cancer treatment. Women who have dyspareunia come to dread and avoid sex. Treatments for cancer survivors can address the risk factors above and incorporate techniques effective in treating desire disorders in other populations.[96]

In addition to sexual counseling, some specific medical techniques are available and will be described in *Tendrils* along with a critical evaluation of their risks and benefits:

- Vaginal dilation: Vaginal dilation is believed to prevent loss of vaginal caliber and elasticity after pelvic radiation therapy.[15] Practice standards in this area vary widely, however, and adherence is quite low, even after a psychoeducational group intervention.[97] Graduated vaginal dilators may be helpful combined with instruction on kegels and using water-based lubricants during sexual activity.[98]
- Estrogen replacement: Cancer survivors are often reluctant to use systemic estrogen replacement.[99] A more acceptable and safe option may be low-dose, vaginal suppositories or rings that reduce vaginal dryness and pain with sex, with minimal escape into the general blood circulation.[100]

- Testosterone replacement: Although randomized trials suggest that testosterone replacement can improve women's sexual desire and pleasure after bilateral oophorectomy,[101] the one study that actually examined androgen levels in postmenopausal women treated for breast cancer found, contrary to expectation, that those with more bioavailable testosterone actually reported less desire for sex.[53] Unfortunately, both high endogenous levels of androgens and use of androgen supplementation are significant risk factors for breast cancer, so that the cost-benefit ratio is questionable.[102]
- Devices to increase genital blood flow: A vacuum device to increase clitoral blood flow, the Eros®, was used for 3 months by 13 women treated with radiotherapy for cervical cancer. The researchers reported dramatic improvements in sexual function, as well as on vaginal examination.[103] The rationale for such improvements is unclear, however, and replication in a randomized trial is needed.

PRELIMINARY STUDIES/PROGRESS REPORT

Expertise in Content. Our team possesses unique qualifications to carry out this project. In terms of content, Dr. Schover has authored much of the current patient education information on sex and cancer, informed both by her extensive clinical experience and her own research on the topic. In 1988, she drafted booklets on sexuality and cancer for the American Cancer Society (ACS) for men and women. They have been updated every several years since, remaining the most popular patient education materials ever produced by that organization, with hundreds of thousands of copies distributed. A few revisions have been made that she does not endorse, such as advocating the use of androgen replacement for women with low desire, but the text remains about 90% faithful to the original. It is available on the ACS website at http://www.cancer.org/docroot/MIT/MIT_7_1x_SexualityforWomenandTheirPartners.asp

Dr. Schover also wrote the sections of the Lance Armstrong Foundation's survivorship LiveStrong information on male and female sexuality and a booklet on ovarian cancer and sexuality for the National Ovarian Cancer Coalition. In 1997, Dr. Schover published a self-help book, *Sexuality and Fertility after Cancer* with John Wiley & Sons. A trade paperback, it has sold approximately 4,000 copies and is currently being remaindered. Despite excellent reviews, it was not well-publicized. It provided more detail in all respects than the ACS booklets and also included chapters on fertility after cancer.

However, printed self-help books and pamphlets have limited impact. Although self-help books are more popular with women, they are primarily read by the college-educated. Twenty percent of Americans read at less than a fifth-grade level and 58% of the US adult population never reads another book after high school.[104] Most book buyers are over age 55. Educated, younger women in their 30s to 50s tend to be the most active information-seekers among cancer patients.[105]Although print materials and health care professionals are still the two top information sources for cancer patients and survivors, use of the internet and multimedia patient education media is growing.[105] Information about sexuality and body image accounted for about 4% of information needs among cancer patients in the literature, with most studies focusing on the period of diagnosis and treatment planning. Sexual function becomes a prominent problem in the longer-term survivorship period, however.[106] Thus Dr. Schover's research in the past few years has focused on developing innovative, multimedia interventions that could provide information on reproductive health to a wider audience of cancer patients, incorporating behavior change strategies as well as didactic information.

Expertise in Sexuality Intervention Research. For the past several years, Dr. Schover has been conducting trials of a peer counseling program in reproductive health (SPIRIT) for African American breast cancer survivors, in partnership with Sisters Network®, Inc., a national advocacy group. The pilot study is currently submitted for publication. Sixty women were randomized to immediate counseling or a 3-month waiting list. Three trained peer counselors conducted a 3-session intervention based on a detailed 77-page workbook, divided into three chapters: Menopause and Breast Cancer (hot flashes, vaginal dryness, urinary incontinence, preventing urinary tract infections and vaginal yeast infections, talking to your doctor); Sexuality and Breast Cancer (feeling unattractive, talking to your partner, resuming sex after cancer, dating, low sexual desire, pain with sex); and Cancer and Your Family (fertility and breast cancer treatment, safety of pregnancy after breast cancer, health of offspring, recognizing familial breast cancer, genetic counseling, and becoming an advocate for cancer screening for family and community). The Flesch-Kincaid Grade Level Score was 8th grade and the Flesch Reading Ease score was 61.2, in the desirable range. African-American themed clipart was used throughout and the workbook was edited for cultural sensitivity. Questionnaires at baseline, after the waitlist period, at post-treatment, and at 3-month follow-up assessed spirituality, sexual function, menopause symptoms, emotional distress, relationship satisfaction, fertility concerns, and knowledge about reproductive health and breast cancer. At the post-counseling assessment, women rated the workbook, their counselor, and the program.

Women who completed counseling (80%, N=48) had a mean age of 49 years (Standard Deviation (SD) = 8). The mean years since cancer diagnosis was 4.5 (SD=3.8). Women valued the SPIRIT program highly and found it relevant. Almost all (94%) rated the workbook as "very easy to understand" and their counselor as very knowledgeable (96%) and skillful (98%). Eighty-one percent rated the program as "very useful to me." The program had positive effects on knowledge and target symptoms. The immediate counseling and waitlist groups did not differ at baseline in psychological adjustment, nor did scores change during the waitlist period. Therefore, the groups were combined in analyses of outcomes. Knowledge of

reproductive issues improved significantly from baseline to 3-month follow-up (P<0.0001), as did emotional distress (P = .0047), menopause symptoms (P = .0128) and sexual function (P = .0306).

Currently, Dr. Schover has RO1 funding from NCI to conduct a national randomized trial comparing the full SPIRIT program with a minimal contact version in which women get the workbook and a "bank account" of up to 30 minutes of phone time with their peer counselor, but no face-to-face interaction. In addition to the other measures, health care utilization and help-seeking for reproductive problems are being assessed. The efficacy of the pilot study suggests, along with earlier studies, that many of the sexual problems experienced after cancer will improve with information and suggestions on self-help coping strategies. The SPIRIT project also demonstrates our ability to partner with advocacy groups and recruit minority cancer survivors.

Dr. Schover also has a Research Scholar Grant from the American Cancer Society to conduct a randomized trial of *CAREss (Counseling on Regaining Erections and Sexual Satisfaction),* an internet-based sexual counseling intervention for couples after the man's prostate cancer. Couples are randomized to a 3-month waitlist control and then to an intervention; or to immediate counseling. In a 3-session face-to-face, traditional counseling condition, both partners receive the same materials as in the internet version, but in print format. A therapist manual details content for each session. The internet condition includes educational information and behavioral homework presented via text, photographs, animations, and video clips. Two couples, one Caucasian and one African-American, tell their own stories in video segments. Participants complete behavioral homework and fill out online report forms which are emailed to their counselor. They receive feedback via email as well. The amount of time they spend on the website, the pages they view, and the percent of the informational and behavioral exercises they complete are recorded electronically. Online bulletin board support groups are available separately for the men and for their partners. A pilot study evaluating the basic face-to-face counseling program is in press in *Cancer* and can be found in Appendix 4. The face-to-face intervention, which took 4 sessions in the pilot version, produced significant improvements in both men's and women's sexual function and satisfaction, although some gains were not maintained at 6-month follow-up. At 6 months men were significantly more likely to be successfully utilizing a medical treatment for their erectile dysfunction compared to baseline.

Multimedia Expertise. The partnership between Dr. Schover at UT M. D. Anderson Cancer Center (UTMDACC) and Dr. Martinetti at AXIS Healthcare Communications (AXIS), has already resulted in the creation of two interactive, multimedia interventions for reproductive health problems after cancer. One is the *CAREss* website described above. The other is *Banking on Fatherhood,* a multimedia educational tool to facilitate decision-making about sperm banking before cancer. It includes separate sections for health care providers vs. for patients and family members, and has been funded by a fast-track R25/R44 grant from NCI. *Banking on Fatherhood* is in the final stages of R44 Phase II evaluation. Pilot studies have shown that both physicians and patients rate it easy to use and relevant. For example, out of 19 oncology fellows and 20 male patients aged 14-45, 100% rated the CD-ROM as easy to understand, and found it easy to find information. Only 1 out of each group rated it as difficult to navigate. Video vignettes and animations were rated highly and added to enjoyment of the product. Physicians who viewed it scored significantly higher in knowledge about cancer-related infertility than those who did not on a 20-item True/False test, and a trend was seen for the same effect in patients, though the difference between groups was not quite significant. Patients who viewed it scored significantly lower in conflict about the decision to bank sperm than a group randomized to fill out the scale before viewing *Banking on Fatherhood*. We are making final revisions and will test the product with health care providers and patients at UT M. D. Anderson over the next few months, comparing knowledge, decisional conflict, decisional satisfaction, and rates of sperm banking to those during a baseline period in which patients only receive a brochure about sperm banking.

Survivorship Education and Marketing Expertise ("Site Administrator"). The NCI Multimedia Technology Health Communication SBIR/STTR program for 2006 requires a "Site Administrator" to address barriers to implementing a new technology. In consulting with Dr. Dresser, she suggested that a survivor advocate would be appropriate for this application, since *Tendrils* will be potentially direct marketed to survivors or to the health care professionals counseling them. Susan Nessim Keeney, founder of Cancervive®, author of two editions of the book of the same name, documentary filmmaker and public speaker, will serve this role. She will be our consultant on implementation of marketing strategies as well as a subcontractor in Phase II, casting and videotaping the 5 survivors' stories for *Tendrils*. Cancervive,® a 501c3 nonprofit organization, has produced a variety of videos on cancer survivorship, focused on survivors

telling their stories. They developed the Cancervive Back to School Kit, a comprehensive package of materials to assist children and adolescents re-entering the school setting, including a teacher's guide and two award-winning documentary videos. All educational materials are tax-deductible and all proceeds go directly back into Cancervive programs. Bruce Postman, Cancervive's Director of Special Projects, will supervise the actual casting and videotaping of the survivorship stories. Mr. Postman, an award-winning film director, producer, and screenwriter, will add his expertise in creating sensitive and informative videos and documentaries about cancer survivorship to the *Tendrils* project. Although the Axis team has the technical ability to create the survivorship stories, we all believe that the collaboration with Cancervive will ensure a viewpoint and level of quality that will justify some added expense.

In addition, we have put together a stellar panel of expert professionals and advocates (see list in Phase I Research Design and Methods) to serve as consultants and rate the ease of use, comprehensibility, and relevance of our programs. Panel members bring expertise in multimedia applications in cancer communications, breast cancer and quality of life, gynecological cancer and quality of life, issues of minority and underserved women, treating women's sexual problems in a major cancer center, special issues of lesbian women cancer survivors, issues of infertility and its effect on women's self-concept and sexuality, cancer diagnosed during pregnancy, cancer patients with psychiatric disorders and sexual dysfunction, and training oncology nurses to provide sexual assessment and brief counseling.

PHASE I RESEARCH DESIGN AND METHODS

Aims. Table 1 presented the aims of Phase I, primary and secondary responsibilities of the UTMDACC team, AXIS team, and the Cancervive subcontractors, and the milestones that will show the tasks are accomplished. **We will consider the project feasible if at least 75% of women in our focus groups and 75% of panel members rate *Tendrils* as easy to use and relevant after viewing text, sample story-boarded animations, and sample scripts for video vignettes. Ratings will be made on an 11-item evaluation form with a criterion score of 22 or less as acceptable.**

Content Development. During Phase I, the team at UTMDACC will develop the actual content of *Tendrils*, including writing text, creating cognitive behavioral exercise instructions and recording forms, working with the AXIS team on the format and captions for at least two sample animations, and writing at least two sample scripts for vignettes to be filmed with actors to illustrate clinical situations, communications techniques, etc. We have collaborated successfully in our two prior projects with most communication via phone and email. The team at AXIS will design the visual look of *Tendrils* and will create the artwork for animation storyboards.

The *Tendrils* Program. *Tendrils* is designed as an interactive product that could be viewed over the internet, on a CD-ROM, printed out (text and illustrations), or downloaded as digital audio or video files to a personal digital assistant or media player. It will be directly marketed to women newly diagnosed with cancer or who are longer-term cancer survivors, and also evaluated as a potential package product for oncology nurses and social workers, accompanied by a therapist manual. The goals are as follows:

- Help women understand how cancer treatments can interfere physically with sexual function
- Help women understand the common emotional impacts of cancer on sexual attitudes and pleasure
- Give women the skills they need to communicate with their health care providers about treatment options
- Give women the skills they need to communicate with their partners about making sex better
- Help women identify and evaluate their options for medical treatment of sexual problems or for professional sexual counseling
- Help women to overcome sexual problems by using self-help strategies
- Allow women to navigate through *Tendrils* in any order that corresponds to their needs, though we will advocate beginning with completing "*My Journey*," and reviewing the sections on basic anatomy, the sexual response, and impact of cancer treatments on sexual function

The concept of *Tendrils* is that even though cancer treatment damages women's sexual function, it is possible to find new ways of enjoying sex after cancer. The image of nurturing new growth, and the sensitive nature of female sexuality will be illustrated in a *Tendrils* theme song.

Table 4. TENDRILS Theme Song

They think they got it all, with their poison and their knife.
They say you're a survivor now— go out and live your life.

But I still feel so tired, so changed and full of dread.
My body has betrayed me once—the sword hangs overhead.

We take the earth for granted; Just a rock beneath our feet.
But it's a spinning planet with a molten core of heat.

I traveled to an island, just for a change of pace.
But the palm trees didn't soothe me and I still felt out of place.

No hula girls or waterfalls could make me feel less sour,
So I went to see volcanoes, to witness nature's power.

We take the earth for granted; Just a rock beneath our feet.
But it's a spinning planet with a molten core of heat.

The Devastation Trail was a world of black and gray.
A graveyard heaped with cinders where the bones of burnt trees lay.

That landscape felt familiar. It mirrored all I'd lost-
A woman scorched and barren—alive at what a cost?

We take the earth for granted; Just a rock beneath our feet.
But it's a spinning planet with a molten core of heat.

And then a color caught my eye—a flash of pink and green.
Tendrils growing on a log, an orchid's silky sheen.

One perfect bloom reminded me what every gardener knows-
The richest soil for growing things comes from old lava flows.

We take the earth for granted; Just a rock beneath our feet.
But it's a spinning planet with a molten core of heat.

Tendrils will include personal stories about sexual recovery after cancer from five female survivors varying in age and ethnicity. At least one woman will be over age 65, one will be lesbian, and one a survivor of childhood cancer. At least two of the women will be from ethnic minorities. Their stories may be viewed either as one narrative with episodes for women who want the whole story at once, and with links to relevant episodes that illustrate a particular issue in a section of *Tendrils* for women who just want to see someone else's personal account on that topic. Casting, videotaping, and editing of the survivors' stories will be subcontracted to Susan Nessim Keeney and Bruce Postman at Cancervive, Inc., because of their unique expertise in producing prize-winning multimedia educational programs for cancer survivors

Tendrils will include a feature called "*My Journey*" that will ask participants to write their own stories, either online or on paper. Although some have theorized that expressive writing would help women cope with cancer, most studies have not found clear benefits in terms of reduced emotional distress.[107] In fact a focus on negative emotions may be detrimental. Here the writing is structured, however, serving as a self-assessment to replace the verbal interview most sex therapists would conduct. Women's emotional distress levels will be monitored periodically in the randomized trial so that we can intervene if necessary, but in *Tendrils* itself, signs of serious depression or anxiety will be described, and suggestions given for finding mental health resources. Each question that prompts the woman to write her story will also be accompanied by three short video vignettes illustrating women survivors' experiences. Vignettes will present coping rather than mastery models, i.e. women who have problems, but use positive cognitions or try new behaviors.

- How old were you when you were diagnosed with cancer? How did your age influence the way cancer affected your sexuality?
- What type of cancer treatments have you had? How have these impacted your sexuality?
- What is your current menstrual status (i.e. Are you still having "periods?" If so, are they regular in timing or irregular? If you are in menopause did that happen as a result of your cancer treatment or naturally?) How does this affect your sexuality?
- How was sex before your cancer started causing symptoms?
- How has your sex life changed since your cancer was found?
- Do you have a regular sexual partner? If so, describe that relationship (or perhaps more than one relationship).
- Had you already had any children you wanted before your cancer was diagnosed? If cancer interfered with having children, how has that affected your sex life?
- How has your religious and/or cultural background affected your sexuality?
- Have you ever had a traumatic experience related to sex, such as being forced into sex against your will or punished for being sexually active? If so, how did that influence your sexuality? Did the cancer experience remind you of bad memories from the past?
- Do you discuss your sexual feelings and attitudes with anyone? If so, describe how open you are with friends or family.

Tendrils will use animations to illustrate anatomy or sexually explicit material. We believe drawings will be acceptable to women who might be anxious or upset by photographs or videos. Animations will include 1) a cross-section of the pelvis, illustrating ovarian hormone production, menstrual cycles, and fertility; 2) the vulva, identifying major parts and their functions; 3) the genital area during sexual arousal, showing changes in blood flow and vaginal expansion and lubrication; 4) changes after menopause contrasted to the normal sexual response cycle; 5) the role of "involuntary" autonomic nerves in the sexual response will be shown and orgasm will be explained, including contractions of pelvic muscles, role of the nervous system, and areas of greatest sensitivity; and 6) the physical impact of cancer treatments on anatomy and sexual response will be illustrated.

Topics addressed with text will include how cancer treatment damages sexual function. In this section *Tendrils* will explain problems associated with premature ovarian failure, direct tissue damage from surgery or radiation therapy, changes in erotic sensation, and damage to physical appearance. Coping strategies will be described in detail to improve women's sexual self-concept, with specific, behavioral exercises recommended. These will include using positive cognitions, healthy lifestyle changes, and enjoying the senses in positive ways (massage, bubble-bath, dance) that make a woman feel more sexual. Although *Tendrils* will not have a major focus on cancer-related infertility, we do want to explain how some

cancer treatments can damage fertility and to discuss issues of coping with a cancer diagnosis during pregnancy, safety of pregnancy after cancer treatment, familial cancer syndromes, health of children born to cancer survivors, and how grief about infertility can impact sexual self-image and feelings. We will discuss how different types of cancer treatment may affect the effectiveness or health risks of particular contraceptives. The relationship of sexually-transmitted infections to female cancer (HPV, HIV) and the importance of safer sex, especially during immunosuppression, will be discussed.

Video vignettes with women of varying ages and ethnicities will be used to illustrate benefit-finding, i.e. ways that the cancer experience can actually lead to positive changes in their sex life. Benefit-finding has been associated with better long-term emotional adjustment in women with localized breast cancer.[108] Video vignettes will also illustrate techniques for communicating with physicians and with sexual partners in an assertive and effective way to resolve sexual problems. Vignettes will be used to present a sexual problem situation that causes distress. Several possible strategies will then be shown as options. When the woman chooses one, the outcome will be played out by the actors. Women will be asked to generate their own ideas about other coping strategies. Actors for vignettes will vary in age and ethnicity, helping to illustrate varying religious and cultural views on female sexuality in a respectful manner.

The most common sexual problems women experience after cancer will be described in video vignettes (monologues or interpersonal situations, not actual sexual activity), including loss of desire, trouble feeling erotic pleasure, having chronic pain (nongenital or genital) that interferes with sex, and difficulty reaching orgasm. Survivors in the vignettes will vary in age, ethnicity, and cancer site. Each of the above problem descriptions will link to an intervention section, or women can navigate through *Tendrils* in the order presented. For loss of desire, intervention topics will include the search for an effective medication, side effects of psychotropic medications, role of fatigue, role of depression, promoting healthy exercise and diet, focusing on positive erotic imagery, finding behavioral conditions that increase interest in sex, setting aside quality time for sexual activity, and being assertive in sexual communication. To overcome genital pain, instructions will be given on use of vaginal lubricants and moisturizers, graduated vaginal dilators, positioning, and pros and cons of low-dose vaginal estrogen therapy. A number of cognitive-behavioral homework exercises will be included, such as desensitization to physical changes by viewing and touching areas while using positive self-statements; working to change negative cognitions that interfere with enjoying sex; using the sensate focus framework to resume sex comfortably; practicing strategies to stop distracting negative thoughts during sex, etc. Standardized forms will be included for women to summarize their experience with an exercise, either to encourage self-review, or to show to a counselor. Throughout, we will mention problems that might occur during homework that should alert the woman that she may need to seek help from a medical or mental health professional. However, our experience with intervention studies has been that adverse events are quite rare.

Types of interventions available from different medical specialists (endocrinologists, gynecologists, sexual medicine specialists) will be highlighted, along with suggestions on finding a specialist and a discussion of insurance issues. Other sections will discuss specific sexual problems related to particular cancer sites or treatments, such as coping with vaginal reconstruction, ostomies, limb amputations, or laryngectomies in sexual situations. A guide to coping with dating issues after cancer will be included for women not in a committed relationship. A section for partners will discuss their needs and how they can be supportive in helping the woman resolve her sexual problem. A section specifically on female couples will be included as well.

Panel of Expert Professionals and Patient Advocates. We have found in our previous research that it is extremely valuable to obtain feedback on our multimedia content and presentation from expert professionals in the field and from patient advocates familiar with particular survivor constituencies. For this project our panel includes the following consultants (see Letters of Support): Lindsay Nohr Beck, founder and Executive Director of the advocacy group Fertile Hope, dedicated to helping cancer survivors become parents; Patricia Fobair, MSW, psychosocial researcher and survivorship advocate, with expertise on the quality of life of lesbian breast cancer survivors; Mary Hughes, MS, RN Advanced Practice Nurse in the section of Psychiatry at UTMDACC, and course leader for an oncology nursing seminar in sexual counseling; Gary Kreps, Ph.D., Eileen and Steve Mandell Endowed Chair in Health Communication, Professor and Chair, Department of Communication, George Mason University in Fairfax, VA, expert in cancer-related health communication; Laereen Lyght, LPN, cancer survivor, Vice-President of the Houston chapter of Sisters Network,® Inc., an advocacy group for African-American breast cancer survivors, and

trained peer counselor for the *SPIRIT* program; Michael Krychman, MD, gynecologist , sex therapist, and director of the female sexual medicine program at Memorial Sloan-Kettering Cancer Center; Andrea Milbourne, MD, Assistant Professor of Gynecologic Oncology at UTMDACC, providing clinical services for gynecologic complications of cancer in female patients; Eva Singletary, MD, breast cancer surgeon, quality of life researcher, and Professor of Surgical Oncology at UTMDACC; and Charlotte Sun, Dr. PH. , Assistant Professor of Gynecologic Oncology at UTMDACC, and researcher on quality of life and decision-making in gynecological cancer patients.

Outcome Measures. Each member of the panel will evaluate the content of *Tendrils* in months 5-6 of Phase I by being given access to a password-protected website presenting the text and sample animation storyboards and vignette scripts. Each panel member will be asked to complete a brief rating form (see Appendix 1) modified from the ones we are already using in the *Banking on Fatherhood* project. It has 11 multiple-choice ratings with a 4-point Likert scale response format ranging from strongly agree to strongly disagree. One version is for expert professionals and one for cancer survivors. Our criterion for feasibility will be that at least 75% of raters score 22 or less (i.e. give favorable ratings on the average to each dimension). If that criterion is not met, we will make suggested revisions and redo the ratings.

Focus Groups. We will conduct also three 90-minute focus groups during months 5-6 at UTMDACC, each with 6 to 8 female cancer survivors. Patients will be recruited with flyers and personal contacts from a variety of areas around UTMDACC, including support groups, patient care areas, patient education areas, the Center for Wellness, and our website for volunteers, Anderson Network. Our Senior Research Coordinator, Lorna Mangus, and Dr. Schover will moderate the groups. Each group will represent a specific age range (18-35, 36-55, and ≥56 years), to ensure that *Tendrils* appeals to a broad spectrum of women survivors. We will also try to maximize variety in educational level, ethnicity, and cancer site among the focus group participants. Focus group participants will be compensated with $50 for their time and trouble, as well as having paid parking or transportation to the medical center. Refreshments will be served. The focus groups will be conducted under a protocol approved by the UTMDACC Institutional Review Board (IRB). Informed consent will be elicited before entry into the focus group study, including information about confidentiality and taping of the group. During the week before the focus group, each participant will be asked to view a *Tendrils* prototype over the internet on a password protected website. She will complete the survivors' written evaluation form, (see Appendix 1) The actual focus group sessions will be audiotaped to make sure recall is accurate for reporting, but hand-written notes will also be kept.

The questions asked in the groups will be the following:

1. Was the information presented clearly?
2. Would you find this program helpful in coping with cancer-related sexual issues?
3. What did you like the most?
4. What aspects of the materials could use revision?
5. Was anything important left out?
6. Did you find the materials tasteful and sensitive to culture and religion?
7. Do you think that most women would feel comfortable learning about sexuality after cancer from these materials?
8. What format would you prefer for different parts of *Tendrils*? (i.e. print, on computer, audio or video downloads, etc.)

Focus Group Analysis. After each group, the moderator and assistant moderator will discuss the experience briefly and add debriefing comments to their field notes. The audiotapes of the groups will be transcribed. The qualitative data will be transcribed, coded and entered into the Ethnonotes/NUDIST data management package. Following data entry, results will be checked for obvious errors and inconsistent values. Participants will be identified in the computer records with a unique coded identifier but not by name. This will enable us to track responses according to participants' ethnicity, cancer site, or educational level. Dr. Schover and Ms. Mangus will collaborate on data analysis.

A content analysis will be conducted using Ethnonotes/NUDIST, a qualitative analysis program. Our Senior Research Coordinator, Ms. Mangus, is experienced in using this software. For each question above, word-specific and content analyses will be performed. The Ethnonotes/NUDIST program allows the researchers to compare responses by SES, medical history, menopausal status and other demographic variables. Summaries of qualitative data will be made based on central themes and key quotes within the

context of the whole text and according to their representativeness and typicality within each group (older vs. younger women, specific types of cancer treatment, higher/lower SES).

PHASE II RESEARCH DESIGN AND METHODS

Aims. The specific aims of the 3 years of Phase II are 1) to use the feedback from Phase I to complete a multimedia prototype of *Tendrils* that is easy to use, easy to navigate, relevant to survivors' sexual concerns, and medically accurate; 2) to test its efficacy in a randomized trial comparing its use on a self-help basis vs. in the context of counseling; and 3) to use the results of the randomized trial to make final revisions before commercialization and to target marketing to the format that is most efficacious, which may differ for specific demographic groups of cancer survivors. Tasks, timeline, and milestones for Phase II were presented in Table 2.

Creative Process for Multimedia Prototype. To fully develop each media piece in the intervention, Paul Martinetti, MD and his creative team at AXIS will work closely with Dr. Schover. The team will use a standard AXIS approach to developing all of the rich media content, including three core components: 1) a description of each step of the interactive piece, including any motion and sound for each active object; 2) a clarification of specific rules of science to which the developers must adhere when developing the interactive content, and a specification of each object to which the rules apply; and 3) explicit ranges and direction for allowable artistic flexibility so that the scientific soundness of the piece will be maintained.

Interactive development and website programming will be done in house at AXIS and will be supervised by a senior producer who is a member of the development team. During the time of interactive development, Dr. Martinetti will be available to answer developer questions. Dr. Schover will be routinely involved in reviewing materials. Much of this communication can be accomplished via Web-based review, email, FAX, and phone contact, but one face-to-face meeting for Dr. Schover to travel to AXIS Healthcare Communications is budgeted in Year 1 of Phase II.

Specific Media Proposed. The following media will be included in our final product.

- **Graphic Art.** Dr. Martinetti will work with Creative staff to design a user interface artistic theme that is appropriate considering the clinical and emotional aspects of the content, and functional needs of the application.
- **Video.** Video will be taken using digital videotape, and edited in the Digital Studio at AXIS. Video clips will be incorporated into the program using industry standard compression and playback formats. At this stage, AXIS envisions 15-25 short, scripted video segments with actors, of 1-5 minutes each. Survivor stories will be casted, taped, and edited by Susan Nessim's team at Cancervive, with Bruce Postman directing, and consultation with Dr.'s Schover and Martinetti.
- **Animation.** Animation will be incorporated in the program using complex 2 and 3-dimensional techniques with Macromedia Flash Professional 8. *Tendrils* will use animations, rather than photos or videos, to illustrate genital and pelvic anatomy and changes to sexual function. We believe this type of presentation will be more acceptable to women who might be anxious or upset by actual depictions of genitals or sexual activity. No sexual acts will be depicted, although some positions for sexual activity may be presented. We anticipate creating 6-8 complex animations.
- **Audio:** Voiceover narration will be used as appropriate to best explain difficult concepts, in conjunction with complex animated sequences. We will commission music and record a female vocalist performing the *Tendrils* theme song. (We have a theme song *Miracles* in our product *Banking on Fatherhood.*)
- **Downloads:** Digital video and audio files will be formatted so that women can download them to a PDA or a media player. Although the personal stories of survivors will be viewable online as videos, the soundtracks will also be available for download in audio format, since women may want to listen to them on a PDA or media player while driving in the car, walking, etc.
- **Printouts:** Text sections will be printable so that women can print them out and read them at leisure. Some women are less comfortable with computers, but it is also helpful to have printed versions of instructions for cognitive-behavioral homework, homework summary forms, etc.

Software Features of *Tendrils*. The *Tendrils* program will be presented for the Phase II randomized trial on a password-protected website. The website will be programmed so that each participant has her own username and password for login. The research staff at UTMDACC will keep a list of participants matched with usernames in a locked file. No names, addresses, or other identifying information will be entered online. The website will be hosted on a UTMDACC server which is protected from hackers by institutional firewalls and other routine security precautions.

The site will be developed using industry standard applications and rendered in a common Web format supported by free, rich media plug-ins. The global data structure standard XML will be used to structure and transfer content and formatting descriptors (metadata). This will allow us to have one master copy of the Tendrils content used by multiple media environments including: Web, CD, mobile, and print. XML also maintains the association of rich media files with their relevant text in the content body. And finally it allows us to offer users a literal-text search function for quick access to desired parts of the program, through dynamic display of text on the screen.

Participants will be informed that their usage of the website will be tracked electronically. The interface will deliver information on each user's activity to a database application. The database can manipulate, compute, organize, and store information gathered from the user interface. AXIS will work with the UTMDACC team to set up the database program, ensuring that data are compatible with planned statistical analyses. We have already successfully implemented such a system for the *CAREss* project. The database application will not be packaged with the marketed product, however.

Tracking will include number and duration of log-ins (if a log-in goes longer than 20 minutes without activity, the participant is automatically logged off of the website), pages visited, pages printed out, and digital files downloaded. In addition, we will ask participants to complete a 3-item weekly online questionnaire estimating the number of minutes that week 1) spent listening to or viewing downloads, 2) reading printouts, and 3) completing cognitive-behavioral exercises presented in *Tendrils*. Although weekly reporting is not as reliable as prompting participants to report at random times via a PDA, as in ecological momentary assessment (EMA),[109] the diary will supplement the real-time monitoring from the website. We do not believe the additional sensitivity of EMA is justified for this project, given its added cost and complexity. To ensure that women are not filling out the diaries in one session near the end of the 12-week treatment period, entries will only be accepted if made within a scheduled 3-day window of time. We will compensate women for completing the weekly entries (see Measures of Time Spent Using *Tendrils* below).

Navigation. The *Tendrils* program will have a home page that will orient women to all of the content, directing access through simple navigation buttons and key presses. In addition we will develop a short orientation animation that highlights and explains the user interface elements and how to use them. Whenever possible, natural patterns of thinking and usability standards will be applied to navigation strategies. Women can navigate according to their preferences. Major topics will be listed along the left side as boxes that will show drop-down menus when clicked with the mouse. A search feature will also allow women to find sections relevant to a particular cancer site, sexual problem, or other relevant terms, for example lubricants, dilators, or dating. A searchable glossary of medical terms or anatomical names will be included, as we have done in *Banking on Fatherhood*.

Product Evaluation at NCI. As required by the Cancer Communications program, *Tendrils* will undergo usability testing and content evaluation at the NCI Technology Center. Funds have been allocated in the budget for this purpose in Period 2.

Randomized Trial of *Tendrils* Alone vs. with Counseling. The aim of the randomized trial is to test the efficacy of *Tendrils* in improving women's sexual function and satisfaction, and to learn whether combining 3 sessions of counseling by a master's-prepared professional with *Tendrils* will result in enhanced outcomes compared to using *Tendrils* on a self-help basis. If counseling does produce incrementally better outcomes, *Tendrils* can be marketed to oncology social workers, advanced practice oncology nurses, and psychologists working with oncology patients as a package with a therapist manual. If counseling does not improve outcomes over and above the self-help condition, it will make more sense to restrict marketing of *Tendrils* directly to patients.

Design Issues for Randomized Trial. Reviewers may wonder why we did not include a "usual care" control group. Such a group would demonstrate that time alone did not ameliorate women's sexual problems. It is already very well-documented that sexual dysfunction in women surviving cancer rarely resolves over time without active intervention. In order to ensure that all participants get a viable

intervention, we have used waitlist control groups in our previous studies. However, we get increased drop-out rates of the most distressed participants during the waiting list period so that the groups are no longer truly randomized, making the results more difficult to interpret. If we fail to find significant improvement in sexual function or satisfaction in the group using *Tendrils* on a self-help basis, we will still have a marketable patient education product that is medically accurate and highly rated by cancer survivors. Perhaps it will not produce significant change, however, in self-rated sexual function and satisfaction. We doubt this will be the case, given positive findings from our other, similar, intervention trials.

We also are not including an "attentional control" for the time that women in the counseling group spend with a professional. Attentional control groups are designed to answer the question of whether counseling works because of nonspecific, attentional effects or because of specific, targeted interventions. That question is not really relevant to our aims. We cannot imagine that sitting down with a counselor and discussing irrelevant topics for three hours would result in improved sexual function and satisfaction for these women. We have a complex intervention with a number of active, educational and cognitive-behavioral components. We want to know whether the extra personal attention of seeing a counselor produces better results than letting women self-tailor the intervention. We realize that the two randomized treatment groups will receive differential amounts of attention from a professional. That is precisely the difference that interests us. Is the extra cost of professional counseling worth the benefit?

Hypothesis: Our primary hypothesis for the randomized trial is that *Tendrils* will produce significant improvements in sexual function and satisfaction whether used on a self-help basis or with brief counseling, but that the group receiving counseling will improve significantly more than the self-help group. Secondary hypotheses are that the incremental improvement with counseling will be greater for less educated women and older women. Time spent using *Tendrils* will be examined as a potential mediating factor in outcome (i.e. attention from the counselor may influence women to spend more time using the *Tendrils* intervention, contributing to positive effects from counseling, or conversely. women who spend 3 hours with a counselor may spend less time using *Tendrils* at home). We will also use statistical analyses to see if either or both intervention groups have significant improvements in sexual desire, emotional distress, and quality of life scores.

We chose age and educational level as independent variables in our design because we believe they are most likely to affect how women's success in using the *Tendrils* program. Although we hope that *Tendrils* will produce significant change in sexual function and satisfaction for a wide range of female cancer survivors, we realize that any intervention has limitations. A better understanding of whether older women or less well-educated women can benefit from *Tendrils,* along with knowledge of their usage patterns may result in revisions to the format or better targeting of our marketing efforts.

We expect that women over age 50 will be more likely to view *Tendrils* online or in printed form, and younger women will be more likely to download audio and video files. For example in a sample of women of varying socioeconomic status (SES), women aged 40 to 70 were randomized to learn about breast cancer screening from a brochure vs. an interactive multimedia tool.[110] Younger women preferred the multimedia format, and also learned more than the older women. This study was published in 1998, however, and older Americans have much more familiarity with the internet and computerized media today.[111] Age is also a factor correlated with health literacy, the ability to comprehend health information in order to make appropriate health decisions.[112]

Educational attainment and health literacy are closely linked. A recent meta-analysis of 85 studies of health literacy showed that about a quarter of research participants had truly low health literacy and another quarter had marginal health literacy. [112] Poor literacy was not associated with gender, but was higher in African-Americans, older adults (i.e. those in their mid-40s or above), and those with less than a high school education. Most studies excluded those with poor English fluency, underestimating the prevalence among Hispanic or Asian immigrant populations. Current widely used tests of health literacy define it very narrowly, for example by accuracy of reading and pronouncing medical terms, [112] whereas a report in 2004 from the Institute of Medicine favors a broader concept including skills in communicating, cultural and conceptual knowledge of health, and ability to differentiate advertising from other health information sources.[113] Therefore we believe that educational attainment is a more useful proxy for health literacy than measuring it directly with existing tests. We hope that women with less education will be able to benefit from *Tendrils* because of the use of animations, videos, and voice-overs as well as text. Our online questionnaire

assessments will include voice-over to help low-literacy women. Using one application is also easier than sorting out the quality of health information on the internet.[114]

Studies of multimedia health interventions suggest, not surprisingly, that those who use them more extensively benefit more.[115] Our experience with the *CAREss* website intervention is that usage varies greatly. Among prostate cancer males and their female partners, respectively, 37% and 34% completed over 75% of the web intervention, 17% and 11% completed 50% to 75%, 17% and 19% completed 25% to 50%, and 29% and 36% finished less than 25%. Although in CAREss, the counselor communicates with the couple via email, and gives phone reminders to those who are not completing the intervention, there is no face-to-face contact. One possibility in the *Tendrils* randomized trial is that women who meet with a counselor will be more motivated to complete their learning and homework by using the website in between sessions. Thus it will be very important to document extent of website usage to see whether it mediates greater improvement in the counseling group. For *Tendrils*, extent of usage will be evaluated by a combination of real-time electronic monitoring of website usage, plus a weekly 3-item record filled out on the website (see Appendix 3) estimating supplemental minutes per week spent 1) reading printouts from *Tendrils* 2) interacting with downloaded digital audio or video files from *Tendrils*, or 3) completing behavioral homework. For statistical analyses, two measures of usage will be separately evaluated: total minutes recorded by the website over 12 weeks, and a composite measure of real-time minutes plus minutes estimated from weekly usage diary entries.

Recruitment of Cancer Patients and Survivors for the Randomized Trial. All human studies research will be accomplished at UTMDACC, one of the largest comprehensive cancer centers in the United States, and consistently ranked first or second in quality by *US News and World Report*. From September 2003 through August 2004, 8,941 new female patients with a cancer diagnosis were registered at UTMDACC. Spanish surnamed women made up 12% of this population, African American women comprised 9%, and other ethnicities 4%, leaving 75% non-Hispanic Caucasian women. In terms of cancer site, 2,026 (23%) had breast cancer and 1,282 (14%) had gynecologic malignancies. Of course many cancer survivors are also seen at UTMDACC, with over 650,000 total outpatient visits in fiscal year 2005. UTMDACC physicians also staff an oncology clinic at the Lyndon Baines Johnson (LBJ) County Hospital that contributes a more underserved population, including many Spanish-surnamed and African American patients. A separate Institutional Review Board oversees research in the county hospital, but we have had other projects approved there and will seek approval for this one. In addition, Houston is the fourth largest city in the United States. According to the 2000 US Census, Harris County, which includes the metropolitan area, has an ethnically diverse population that is 42% non-Hispanic white, 33% Hispanic, 18% non-Hispanic black, and 7% other (mostly Asian with large Chinese, Vietnamese, Korean, and South Asian communities). We have recruited cancer survivors for other projects from the community using church-based cancer ministries, community health fairs, and public service announcements on local radio stations or in newspapers. Letters and flyers also will be sent by mail to cancer survivors in our tumor registry who fit the study eligibility criteria.

Inclusion and Exclusion Criteria. Although *Tendrils* is designed to be relevant to women with the whole range of cancer sites, stages, and treatments, from diagnosis through to end-stage disease, we will restrict our sample for the randomized trial to survivors of localized breast or gynecologic cancer. We want to have adequate statistical power to examine the influence of age, education, and extent of usage on outcome, without having too many covariate factors to consider. Both breast and gynecological cancer survivors have high rates of sexual dysfunction that do not decrease over time.[20,21,28,29,39] In contrast, other emotional distress associated with cancer tends to diminish after the first year, leaving women with good overall quality of life.[21,22,27,28] Therefore, women who have finished cancer treatment 1 to 5 years previously should be an ideal target group, with sexual dysfunction likely to be their most distressing cancer-related problem. To be eligible, women must be currently free of known cancer, and off active treatment except for hormonal therapies. They must have a sexual relationship of at least 6 months' duration to maximize the chance that they will have a sexual partner available during their 9-month participation in the study. Lesbian women will be eligible. Women will also need to meet our screening criteria for sexual dysfunction, i.e. a total score of less than 26.55 on the Female Sexual Function Index (FSFI) (see below for a full description of measures).[116] Women who are currently having mental health care for a sexual problem will not be eligible to participate. Women must agree to be randomized either to the self-help or counseling condition. This necessitates their living within commuting distance of UTMDACC so that they can attend their 3

counseling sessions. In 2004, about one-third of new female patients with a malignancy seen at UTMDACC lived in commuting distance, giving us a large pool of survivors in our tumor registry for recruitment. Women will need to have access to the internet at home or in another routinely accessible, private location, although we do currently have 10 notebook computers with CD-ROM drives that are available for loan, and we could subsidize internet access in case of need. Current estimates are that over 75% of households in the US have internet access, with almost half having broadband.

We will recruit an equal number of cancer survivors (N =120) with breast vs. gynecological cancer, and within each of those broad diagnostic categories, will aim for 30 women in each of two age groups: 18-49 vs. ≥ 50 years. In 2004, for women 18-49, 767 new patients with breast cancer were seen at UTMDACC, and 455 new patients with gynecological cancer were seen. For women age 50 and over, the total new patients was 1,259 with breast cancer and 847 with gynecologic malignancies. Even if only 1/3 of these women live in commuting distance, 70% had localized disease, and half had sexual dysfunction, we would have at least 50 available from one year in each of our four target groups, and we can contact women from 5 years of the tumor registry, just from our own institution.

We will also try to recruit at least 20% of women with high school educations or less (N = 48) and 20% (N = 48) with some college, but not a 4-year degree. Statistics from the 1990s show that 52% of high school graduates are at best marginally literate.[117] We are not attempting to recruit a higher percentage at these educational levels because our experience has been that most participants in our psychosocial studies have some college education, despite efforts at community outreach to underserved and minorities. For example in our *SPIRIT* study of African-American breast cancer survivors, only 8% had high school education or less, and in the *CAREss* pilot study of prostate cancer survivors and partners, only 14% had that level of educational attainment. The need to have internet access will further complicate recruitment of less educated women. We plan to seek approval to recruit women from the oncology clinic at the county hospital, however, and we also have an excellent collaborative relationship with the Houston chapter of Sisters Network,® Inc. because of our *SPIRIT* study, which will be completed by the time the randomized trial begins, giving us entrée into the local community of African American breast cancer survivors, including a greater percentage of women without a college degree than in our patient population. UTMDACC also has a contract at with Harris County to administer radiation therapy for cervical cancer, and that group of patients also tends to be more diverse and less well-educated.

Adaptive Randomization. We will assign women to the two treatment conditions using a form of adaptive randomization called minimization.[118] Minimization is similar to stratification in that participant characteristics are used to assign participants to the treatment conditions. However, minimization results in better group balance with respect to the participant characteristics and does not suffer limitations found in stratification. In minimization, before a participant is assigned to a treatment group, the total number of participants in each treatment group with similar covariate characteristics are totaled, based on marginal sums so that each covariate is considered separately. The treatment assignment for a participant is then based on which treatment group would have the best overall balance. Minimization provides for balanced treatment groups throughout the randomization process, unrelated to time of accrual. Variables to be used in the minimization will be education (4-year college degree or more less vs. no college degree), age (≤ 49 vs. ≥ 50), current menopausal status, cancer site (breast vs. gynecological) and sexual orientation

Procedures. Women who are interested in the study after receiving letters, flyers, or information from their oncology physician, will contact the study research coordinator (Lorna Mangus). She will perform a telephone screening of eligibility, including screening for sexual dysfunction by administration of the 19-item FSFI. She will also review the informed consent form. Women who are eligible will be mailed the informed consent form. When the completed packet and signed informed consent are returned, women will be minimized to one of the two groups and given a username, password, and the URL of the *Tendrils* website with instructions to complete the baseline questionnaires online. By 2007, the internet-based version of the Questionnaire Development Software (QDS-Web®) from Nova Research will be available. We will use it to create an online interface using an audio computer-assisted self-interview (ACASI), which helps to minimize problems with low literacy. If women do not log on to the website within 2 weeks, they will receive a reminder phone call to assess any barriers that may be occurring. If women do not log on within 4 weeks, they will be considered drop-outs from the study. Women in the self-help group will have to complete the baseline questionnaires (at least 75% of items) to access the rest of the website, and then their12-week intervention period will begin. If a woman is assigned to the counseling group, she will need to

complete the baseline questionnaires in order to schedule her first counseling appointment. Women in the counseling condition must complete their 3 sessions within a 12-week period. Sessions will be conducted in the Behavioral Research Treatment Center, a clinic area created for our department and opened in 2005. Fifteen consultation rooms are available for counseling. Participants will be reimbursed for parking at UTMDACC, or if they take public transportation, for their bus or light rail fare.

Counseling Intervention. A counselor manual will be created with specific topics and tasks for each of the 3 counseling sessions. This manual will be a useful resource in itself, if we market Tendrils to health professionals as a package. We have produced similar manuals for *SPIRIT* and *CAREss*. For *SPIRIT*, which utilizes peer counselors, the manual includes examples of taped role plays illustrating good vs. poor listening and reflection skills. We may create a similar CD-Rom for this manual. For the manualized treatment, Session 1 will focus on understanding how the woman's cancer treatment has changed her sexual function and satisfaction. The counselor will attempt to ensure that she understands any medical factors that contribute to her sexual dysfunction and potential medical treatments that could alleviate them. If she is not comfortable and familiar with genital anatomy, she will be counseled and educated on understanding her body. If needed, she will be coached in how to be assertive with physicians in getting the help she needs. Specific behavioral homework will be assigned, relevant to her specific sexual problems. Session 2 will focus on communication with a partner, being assertive in initiating sexual activity, and in requesting the kind of stimulation that would make sex more pleasurable. Homework will include touching exercises to try with a partner (sensate focus). Session 3 will focus on sexual self-concept, including how a woman's personal family, cultural, and religious history has shaped her attitudes about sexuality, how cancer has altered her view of her own attractiveness, and her ideal view of herself as a sexual person.

Counselor Training and Responsibilities. We are requesting funding to employ a half-time master's level counselor for 15 months from month 9 to 24. The first three months of this period will be devoted to counselor training, since sexual counseling demands some specialized knowledge of anatomy, the sexual response cycle, sexual diagnoses, and sex therapy techniques. If 120 women complete 3 sessions apiece across a year's time, we would anticipate approximately 7-8 sessions per week on average. With paperwork and scheduling, the counselor should occupy about 20 hours a week. Often the intervention is not evenly spaced, and the counselor will also be able to help with coordinating appointments, reminder calls about filling out questionnaires or weekly diaries, etc. The master's-level counselors will be supervised by Dr. Schover, who is a clinical psychologist licensed in Texas. The counselor will carry a pager in case of any mental health emergencies. Participants in both treatment groups will be given this pager number to call if they are feeling distress related to the study. The counselor can then in turn contact Dr. Schover or another licensed faculty member in our department. We have an on-call plan in the new Behavioral Research Treatment Center. Our experience has been that very few crises occur in our short-term sexual counseling intervention studies, however. The counselor will also be trained to identify any complaints reported by participants that should be addressed by a gynecological consultation, such as persistent vaginal pain or bleeding. Our Department of Gynecology has several faculty who only assess and treat gynecological complications of cancer-treatment, such as menopause symptoms, vaginal atrophy, or benign genital problems, etc. We will offer such consultation to participants, but some may not have insurance coverage for these services. In that case we may refer them to our oncology clinic at the county hospital or to other lower-cost community settings such as Planned Parenthood.

Quality Control of the Counseling Intervention. Dr. Schover will hold supervision sessions with the counselor at least every 2 weeks, depending on participant volume. Ten percent of sessions will be chosen randomly to be videotaped (i.e. target 36 sessions, 12 Session 1, 12 Session 2, and 12 Session 3). By the starting date of Phase II, all rooms in the Behavioral Research and Treatment Center will be equipped with digital videotaping equipment. Each of the three tapes will be divided into 10-minute segments. Each segment will be rated (either by Dr. Schover and Ms. Mangus) as to whether the content follows the manual for that session. Inter-rater reliability will be established for Dr. Schover and Ms. Mangus. If less than 80% of a session's content agrees with the manual, the counselor will receive further training. Participants assigned to the counseling condition will be informed that some sessions may be taped to ensure quality control. Verbal permission to tape any session will be elicited from participants, however, in addition to the previous informed consent

Measures of Time Spent Using *Tendrils*. In addition to being informed of electronic tracking of their website usage, including creation of printouts and downloads, women will be asked to complete weekly online diaries (3 multiple choice items, see Appendix 3) estimating minutes during the week spent 1) reading printed out materials, 2) using digital downloads, and 3) completing homework exercises. If a woman does not fill out her diary within 3 days of the due date, her response will not be counted for compensation. Women will be compensated for completing the diaries with a retail store gift certificate as follows: 12 completions: $20, 6 or more completions: $10. In addition, each weekly diary will include a "bonus" multiple choice knowledge question drawn from information in *Tendrils*. Women who get 10/12 correct will get an additional $20 gift certificate. Women who get 7-9/12 correct will get an additional $10 certificate. Women will complete questionnaire assessments on the website at the end of the 12-week treatment period and again at 3-month and 6-month follow-ups. Questionnaires will be identified with a participant number, and not by name. Each time a woman completes her post-baseline questionnaires, she will receive a $20 gift certificate to compensate her for time and trouble. Thus if a participant completes all assessment materials and has a high score on the knowledge questions, she can be compensated a maximum of $100.

Questionnaire Assessments. Four relatively brief questionnaires will be completed by each participant at baseline, after the 12-week treatment period, and at 3- and 6-month follow-ups. At each time-point, the questionnaire assessment is estimated to take 30-45 minutes. The baseline questionnaire (see Appendix 2) will include some introductory items on demographic and medical background. The primary outcome measure will be the total score on the Female Sexual Function Index (FSFI), a 19-item multiple-choice questionnaire measuring 5 domains including sexual desire, arousal (both subjective and physiological), lubrication, orgasm, satisfaction, and pain.[116,119] It takes 10-15 minutes to complete. Validation studies on sexually dysfunctional and matched control women aged 21 to 70 have demonstrated excellent internal consistency (0.89 to 0.97) and 2-4 week test-retest reliability (0.79 to 0.88) for each subscale. Discriminant validity was significant for all subscales as well as the summary score. The full scale score for sexually dysfunctional women had a mean of 19.2 and Standard Deviation (SD) of 6.63, compared with a mean of 30.5 and SD of 5.29 for controls.[118] More recently a cross-validation study used receiving operator characteristics curves in a large sample of women with multiple types of sexual dysfunction compared to controls to develop a clinical cut score (26.55 total score) that differentiated 71% of women correctly.[116] In our SPIRIT study, breast cancer survivors' mean baseline FSFI total score was 17.85 ± 11.57, increasing slightly but significantly after peer counseling to 19.42 ± 11.81. In the CAREss pilot study, for wives of prostate cancer patients, the baseline mean total FSFI score was 15.9 $\pm$ 10.6. After 3 sessions of sexual counseling, scores improved significantly to a mean of 25.1 + 7.6, even though this is still in the slightly dysfunctional range. Thus a change of 1 SD is clinically meaningful on the FSFI. We will have women repeat the FSFI online for the baseline assessment, even though they will have answered it over the phone for the screening process. Several weeks may elapse between phone screening and completion of the baseline questionnaires. It is also possible that responding to a live interviewer would change women's scores on the FSFI compared to ACASI administration.

One problem with the FSFI is that women who are not sexually active with a partner in the past 4 weeks score very poorly. Yet, sexual desire may be present, even for women who lack a partner or were not recently active. The Menopausal Sexual Interest Questionnaire (MSIQ) is a 10-item scale developed specifically to assess problems of desire in postmenopausal women, with 5 items comparing sexual function currently with that before menopause.[120] The great majority of breast cancer survivors who are sexually dysfunctional are menopausal, and therefore, we will use the MSIQ to supplement the FSFI. The MSIQ has excellent internal consistency and test-retest reliability. It takes 5 to 10 minutes to complete and generates 3 subscales of desire, responsiveness, and satisfaction. It discriminates between women with low sexual desire (mean total MSIQ score 23.3 ± 9.42) and controls (mean 48.7 ± 7.73). MSIQ scores were sensitive to improvement in sexual function in women with low desire participating in a randomized, double-blinded trial of estrogen/androgen oral medication vs. estrogen alone. Women classified as "responders" to the androgens had a mean score change of 15.83 (Standard Error of the Mean (SEM) of 1.40) compared to a change of -0.18 (SEM 0.54) in nonresponders. As with the FSFI, changes of less than 1 SD may not be very clinically meaningful on the MSIQ.

To evaluate emotional distress, we will use the BSI-18,[121,122] an 18-item short form of the BSI that includes items from the subscales measuring Somatization, Depression, and Anxiety, as well as a Global

Severity Index (GSI) summary score. The BSI-18 is copyrighted, and if we cannot get permission to administer the hand-scored version in the QDS-Web® format, we may need to mail it back and forth. The BSI-18 takes 4 minutes to complete, correlates highly with analogous scores on the longer versions (the correlation between the GSI on the BSI-18 and SCL-90 is 0.93), and has norms based on 741 women oncology patients, including 298 with breast cancer. Not only is it a useful measure of emotional distress across time, sensitive to intervention effects, but it is very useful in identifying research participants who fit the criteria for "caseness" and may be in need of further psychological assessment. We will score the BSI-18 within 48 hours of receiving a questionnaire packet, and if a woman meets "caseness" criteria, the Senior Research Coordinator or counselor will contact the participant by phone to see if she has adequate social support and mental health services. Dr. Schover will be consulted as well. If a participant needs mental health services, we will give her an appropriate referral or intervene as needed if we feel there is any imminent danger of her harming herself or others. These procedures will be described in the informed consent process. The GSI is a standard T-score with a mean of 50 and SD of 10. Typically, a difference of 1 SD is clinically meaningful, with 2 SD's above the mean indicating clinically significant distress levels.

Sexual dysfunction can have a negative impact on overall quality of life. In fact sexual problems are among the most frequent concerns of long-term cancer survivors.[123] Until recently, there was not a well-designed questionnaire assessment of quality of life for this population, but a new 47-item inventory, the Quality of Life in Adult Cancer Survivors (QLACS) form, has been published, including normative scores for 44 breast cancer and 34 gynecologic cancer survivors.[123] It includes 5 cancer-specific domains (appearance concerns, financial problems distress over recurrence, family-related distress, and benefit-finding), and 7 generic domains (negative and positive mood, cognitive problems, sexual problems, pain, fatigue, and social avoidance). All domains have good internal consistency. The QLACS is designed for repeated follow-up assessments. Although it was normed on a sample of ≥ 5-year survivors that was 58% female, 85% Caucasian, and mostly above age 60, the domains are quite relevant for survivors who have finished cancer treatment more recently. We include it as a measure of overall quality of life, particularly to see if the QLACS improves if sexual dysfunction is successfully ameliorated. Changes over time in the QLACS for intervention studies have not yet been documented in the literature.

Data Management and Statistical Analysis. Ying Yuan, Ph.D. will serve as co-investigator, directing biostatistical aspects of this project. Our Statistical Analyst, Dawen Sui, M.S. will oversee quality control for data management and conduct actual analyses. Data for Phase II will be collected electronically over the internet, either as part of the backend programming of the *Tendrils* website, or in a QDS-Web® ACASI interface. QDS Warehouse databases can be easily exported into SPSS or SAS for statistical analysis. We already own site licenses for the basic QDS system, which now includes encryption of data to further protect its confidentiality. Databases will be stored in a centralized location on an institutional server, with access limited to specific users at the discretion of the project director. The server will be backed up daily. Audits of selected subsets of data will also occur regularly. Privacy safeguards will include appropriate password protection and physical security for all computer systems. In the database, each participant will be identified only by a number. The list linking personal names or addresses to participant numbers will be kept in a separate file and encrypted, so that it is not possible to use medical or background information to identify an individual who participated.

In all statistical analyses, the major time points of interest are the baseline vs. follow-up assessment points (immediate post-intervention, 3-month, and 6-month follow-ups), but the most crucial time to assess change is post-intervention, since our past research has shown that the greatest improvement in sexual function is usually measurable at that point. The 3- and 6-month assessments will be compared to baseline and post-treatment points in order to estimate whether improvement is maintained across time. In our *CAREss* pilot study and other longer-term follow-ups of sex therapy,[96,97] gains made at the end of the intervention sometimes regress to the mean by 6-month follow-up. Separate sets of analyses will be conducted for the primary criterion variable (e.g., sexual function/satisfaction assessed by FSFI score) and the three secondary outcomes (MSIQ total score, BSI-18 GSI, and QLACS total score).

Primary Hypotheses: The major hypothesis of the randomized trial is that *Tendrils* will produce significant improvements in sexual function and satisfaction whether used on a self-help basis or with brief counseling. However, counseling will enhance treatment outcomes, so that the group receiving counseling will improve significantly more on the FSFI total score. The same impact of

treatment will also be seen on measures of sexual desire (MSIQ), general psychological distress (BSI-18 GSI), and quality of life (QLACS).

The analyses will be conducted using a linear mixed model (LMM) using proc mixed in SAS. LMM is widely used in analyzing correlated, longitudinal data because of its ability to incorporate random effects characterizing heterogeneity among subjects.[124] In order to detect the improvement of FSFI score within and between groups (counseling vs. self-help) from baseline to post-intervention, the FSFI total score will be regressed onto time period (baseline to post-intervention), treatment group (self-help vs. counseling), and their interaction, with time period treated as a random effect. Random effects of time will be tested utilizing suitable variance covariance structures, in order to find the best fit for the model. A significant interaction would indicate different degrees of improvement on FSFI score in the two groups. In addition, the slope of the regression line of each group will be computed and tested to examine the significance of the improvement over time. If minimization fails to balance the two randomized groups on particular demographic or medical factors, they will be included as covariates in the analysis.

To examine if the change of FSFI score is maintained over time, we will use similar LMM analyses, but will include three repeated measures (immediate post-intervention, 3-month, and 6-month follow-ups). The baseline measure will be treated as a covariate since our major goal is to determine whether the change in FSFI score is maintained over time. The Tukey-Kramer test will correct the means for multiple comparisons in post hoc analyses. Similar analyses will examine the effects of the two treatment groups across time on secondary questionnaire measures, including the MSIQ, BSI-18 and QLACS domains.

Secondary Hypotheses. We predict that the incremental benefit of counseling will be greater for women who have less education (less than a college degree) or are in the older age group (over 50), i.e. that education and age will moderate the outcome of the intervention. Time spent using *Tendrils* will be examined as a potential mediating factor in outcome, since personal contact with the counselor may increase women's motivation to interact with the website.

Moderator analysis. Baron and Kenny,[125] define a moderator as "a qualitative or quantitative variable that affects the direction and/or strength of the relation between an independent or predictor variable and a dependent or criterion variable." A basic moderator effect can be represented as an interaction between two independent variables. We will use separate linear regression analyses focusing on age and on education. The change in total FSFI score from baseline to post-intervention will be regressed onto the treatment groups, age and their interaction. A similar analysis will focus on education. F tests will be used to test the significance of the interaction. Relative plots and other statistics will explore whether there is an incremental improvement with counseling for less educated women or for older women. Since older participants may also be the least educated, partial correlation may be used to estimate the relative impacts of the two moderators.

Mediator analysis. Two variables measuring participants' extent of usage of *Tendrils* will be created and tested separately in statistical analyses. Particularly if there is a significant difference in outcome between the two treatment groups, we will explore whether the amount of usage of *Tendrils* may contribute to the differential efficacy. We also will examine whether utilization time is a predictor of intervention success independent of treatment group. The two variables will be: 1) the electronic record from the *Tendrils* website of the total amount of time women spend logged in across the 12-week intervention period; and 2) that number plus the woman's total estimate of time spent using *Tendrils* from her weekly diaries. Although the first variable is inherently more reliable since it is recorded in real time, the second variable adds important variability that may come from women's investment of offline team spent reading printouts of *Tendrils*, listening to audio or watching video digital files, or carrying out behavioral homework assignments.

Analyses will evaluate whether amount of usage of Tendrils mediates outcome success of the two treatment groups (outcome variable: change in FSFI score from baseline to post-intervention) will employ the criteria described by Baron and Kenny[125] and elaborated by MacKinnon.[126] In order to examine the mediating effect of the amount of usage on the change of FSFI score, four separate criteria must be satisfied: 1) treatment groups must be significantly associated with a change in FSFI score; 2) the amount of website utilization must be significantly different between treatment groups ; 3) the amount of utilization must be significantly associated with change in FSFI score after controlling for the treatment groups; and 4) the relationship between treatment group and change in FSFI must be significantly attenuated or eliminated in the presence of the mediator. Following the methodology suggested by In accordance with the

methodology detail by MacKinnon[126] and Brown,[127] the four criteria to assess mediation will be examined in simultaneous model and parameter tests using Structural Equation Modeling (SEM) software (e.g., EQS, AMOS). SEM provides a flexible approach to modeling means, covariance, and correlation structures that yields relevant effect estimates (direct, indirect, and total) and standard errors for all of the parameters of interest in mediator analyses.[127,128]

Type of media usage will also be examined in exploratory analyses. Women will be categorized according to the number of pages they print out, the number of audio files they download, the number of video files they download, and the number of pages they view online. Data will be examined to see if patterns of usage can be identified, i.e. women who predominantly use print media, women who predominantly use online media, or combinations. If possible, composite categories will be created to simplify analyses, rather than analyzing each type of media usage separately.

For all modeling procedures (mixed model and ordinary least squares), whenever it is necessary and (or) appropriate, distributional assumptions will be evaluated and normalizing transformations or robust procedures will be used. Standard methods of model diagnostics will be used to determine and address the form of the covariances, transformations, collinearity, and influential observations. Corrections for multiple comparisons across sets of tests will be made. To prevent inflated Type I error rates, we will use a numeric adjustment procedure recently introduced by Westfall and Young,[129] in which bootstrap resampling is used to make corrections to sets of hypothesis tests based on the actual data obtained from the study. Using this approach, the correlations observed in the data are retained in the correction procedure, achieving the desired overall Type I error rate without loss of power due to overcorrection.

Missing Data and Drop-outs. Our previous experience with sexuality intervention studies suggests the attrition rate will be over 20% by 6-month follow-up. LMM is designed to handle such missing data and will give unbiased estimates of effects provided that the covariates in the model fully account for the probability of having missing data. We will check this assumption by looking at the predictors of missing data points. We will also perform analyses to examine whether participants who drop out of the study differ from those who do not in medical, demographic, or psychosocial characteristics. A receiver operating characteristic (ROC) curve may be used to explore the relationship among variables for a variety of different cut points, allowing determination of the factors associated with dropping out.

Power Calculations and Sample Size. We will recruit 120 participants in each treatment condition. Based on our experience with the SPIRIT and CAREss intervention studies, we anticipate a 10% attrition rate by post-intervention, and a 25% attrition by 6-month follow-up. The following power calculations are based on the anticipated sample size of 90 participants in each treatment group remaining by 6-month follow-up assessment. On our questionnaire measures, we are interested in being able to detect relatively large changes of about 1 SD. Using a two group t-test with .05 one-sided significance level, a sample size of 90 in each group will have 80% power to detect a difference of 0.372 SD units between the two treatment group means at each follow up time point. If covariates account for 50% of the variance, we will have 80% power to detect a between-group mean difference of 0.263 SD units.

In repeated measures LMM analyses, detectable between-group effect sizes vary with the correlation between repeated measures. As correlations increase, the minimum detectable between-group effect size also increases (i.e., we have less power). Assuming data from three repeated measures, and using a homogeneous, between-repeated measures correlation of 0.3, the two-group repeated measure LMM analysis will have 80% power to detect an 0.34 SD difference between the two group marginal means; an 0.14 SD increment in means from one time point to the next; and an interaction between groups and time corresponding to between-group differences of 0.28 SD and 0.56 SD at each of the 3 time points. In contrast, if we assume a high homogeneous between-repeated measures correlation of 0.9, the two-group repeated measure LMM analysis will have 80% power to detect an 0.41 SD difference between the two group marginal means; an 0.053 SD increment in means from one time point to the next, and an interaction between groups and time corresponding to between-group differences of 0, 0.11 SD and 0.22 SD at each of the 3 time points. In summary, even with a fair amount of participant attrition over time, LMM analyses of the questionnaire data should have excellent power to detect the clinically meaningful change of 1 SD in our study.

E. HUMAN SUBJECTS RESEARCH

1. Protection of Human Subjects

a. Human Subjects Involvement and Characteristics- Phase I

All human subjects research will be performed at the UT M. D. Anderson Cancer Center (UTMDACC). In Phase I, 24 female cancer survivors will rate the prototype of *Tendrils* and then will participate in a 90-minute focus group. We hope to recruit 6-8 women for each group. Each group will represent a specific age range (18-35, 36-55, and ≥56 years), to ensure that *Tendrils* appeals to a broad spectrum of women survivors. We will also try to maximize variety in educational level, ethnicity, and cancer site among the focus group participants. They will need to be well enough to review the website and come to the UT M. D. Anderson Cancer Center for the focus group, and to speak and read English well enough to understand the materials and communicate in group. There are no other exclusion criteria.

b. Sources of Materials – Phase I

Each participant will complete an 11-item Cancer Survivor Evaluation form with 4-point Likert scale response format, after viewing the *Tendrils* prototype on a website (see Appendix for form). The form will only be labeled with a participant number, and not with any other identifying information. The focus groups will be audiotaped, with informed consent of the participants. The tapes will be transcribed, but any identifying information, such as a woman's name, will be replaced with her participant number. The list of participant names with numbers will be encrypted and kept in a computer database only accessible to the PI and Senior Research Coordinator. After the focus group data is analyzed, the list will be destroyed. If any publications result from this phase, no identifying information about an individual will be included.

c. Potential Risks – Phase I

This research does not pose any clear physical risk to participants, although any research may have unforeseen risks. Women will be asked to discuss sensitive material, i.e. sexual problems that women experience after cancer treatment. Some participants may find this embarrassing or emotionally distressing, but given that they will be informed in advance of the subject nature of the project, women who do not want to discuss sexual issues are unlikely to participate.

2. Adequacy of Protection against Risks- Phase I

a. Recruitment and Informed Consent – Phase I

Participants in Phase I will be recruited mainly through flyers placed in outpatient areas of UTMDACC, public service announcements, or through our volunteer Anderson network. Women from the community may also participate, and special efforts to ensure participation of minority and underserved women may include using our community contacts to inform cancer survivors of desired age or ethnicity about the study. To minimize visits to our institution, women will discuss the elements of informed consent over the phone with our Senior Research Coordinator, and then may complete the written informed consent form, approved by the UTMDACC Institutional Review Board (IRB) by mail or in person, as convenient. Women will need to have signed the informed consent form before they will be able to access the website or participate in a focus group. The informed consent form will conform to our extensive institutional format, and will include a discussion of confidentiality protections for the rating forms and audiotapes from the group. Participants will be compensated with $50 for their time and trouble, as well as having paid parking or transportation to the medical center.

b. Protection against Risk – Phase I

If any participant becomes distressed during the course of the study, the PI will meet with her and make sure that she has a referral for appropriate mental or medical health care. There are no alternative procedures other than not participating. In the introduction to the focus group, the facilitators will emphasize that some women may reveal sensitive information, and that all participants are requested to respect confidentiality and not discuss identifying material outside of the group. The protections of confidentiality in our database are standard for our research and conform to both institutional and Health Insurance Portability and Accountability Act of 1996 (HIPAA)regulations.

3. Potential Benefits of the Proposed Research to the Subjects and Others – Phase I

Participants in Phase I may learn some helpful information from viewing the prototype or sharing their views with other survivors, but also may not benefit at all from participating. However, this is a very low risk study, and the potential benefits to future patients far outweigh the minor risks.

4. Importance of the Knowledge to be Gained – Phase I

This research is important because an estimated 3 million women cancer survivors in the United States suffer in the long-term from sexual dysfunction related to their cancer treatment. There are currently few good patient education materials available, and access to mental health or medical treatments for these problems is also limited by lack of trained professionals, stigmatization of seeking help for a sexual problem, and limited insurance coverage. Creating a multimedia intervention for these problems will give many more women access to needed information, and should empower women to resolve sexual problems by using self-help strategies or seeking appropriate professional care. Phase I will help us ensure that the content of the intervention is useful and easy to understand.

5. Data and Safety Monitoring Plan – Phase I

Phase I does not include a clinical trial.

1. Protection of Human Subjects

a. Human Subjects Involvement and Characteristics- Phase II

All human subjects research will be performed at the UT M. D. Anderson Cancer Center (UTMDACC). In Phase II, we will recruit an equal number of cancer survivors (N =120) with breast vs. gynecological cancer, and within each of those broad diagnostic categories, will aim for 30 women in each of two age groups: 18-49 vs. ≥ 50 years. We will also try to recruit at least 20% of women with high school educationsor less (N = 48) and 20% (N = 48) with some college, but not a 4-year degree. Other inclusion criteria are that participants must have finished cancer treatment 1 to 5 years previously, must be currently free of known cancer, and off active treatment except for hormonal therapies. They must have a sexual relationship of at least 6 months' duration to maximize the chance that they will have a sexual partner available during their 9-month participation in the study. Lesbian women will be eligible. Women will also need to meet our screening criteria for sexual dysfunction, i.e. a total score of less than 26.55 on the Female Sexual Function Index (FSFI), ascertained by administering the questionnaire as part of telephone screening. Women who are currently having mental health care for a sexual problem will not be eligible to participate. Women must agree to be randomized either to the self-help or counseling condition. This necessitates their living within commuting distance of UTMDACC so that they can attend their 3 counseling sessions. Women will need to have access to the internet at home or in another routinely accessible, private location, although we do currently have 10 notebook computers with CD-ROM drives that are available for loan, and we could subsidize internet access in case of need. Women must speak and read English well enough to understand the basic materials and complete questionnaires.

b. Sources of Materials – Phase II

Electronic tracking will record each participant's usage of the *Tendrils* website during the 12 weeks of the treatment period, including time spent online, pages viewed, and creation of printouts and downloads. Women will be asked to complete weekly online diaries (3 multiple choice items) estimating minutes during the week spent 1) reading printed out materials, 2) using digital downloads, and 3) completing homework exercises (see Appendix). Women will complete questionnaires at baseline, after the 12-week treatment period, and at 3-month and 6-month follow-ups. Questionnaires will be completed online, through an interface using Questionnaire Development Software (QDS). Data will be encrypted and stored on an institutional server protected by a firewall. Participants will be identified only by number in the database. The questionnaires will include some demographic and medical background information at baseline. At each assessment point the questionnaires will take approximately 30-45 minutes to complete. Standardized scales will include: The Female Sexual Function Index (FSFI), a 19-item multiple-choice questionnaire measuring 5 domains including sexual desire, arousal (both subjective and physiological), lubrication, orgasm, satisfaction, and pain; the Menopausal Sexual Interest Questionnaire (MSIQ), a 10-item scale

developed specifically to assess problems of desire in postmenopausal women, with 5 items comparing sexual function currently with that before menopause; the BSI-18, an 18-item measure of psychological distress in the past week with norms for oncology patients and community dwellers; and the 47-item Quality of Life in Adult Cancer Survivors (QLACS) inventory, including 5 cancer-specific domains (appearance concerns, financial problems distress over recurrence, family-related distress, and benefit-finding), and 7 generic domains (negative and positive mood, cognitive problems, sexual problems, pain, fatigue, and social avoidance). The list of participant names with numbers will be encrypted and kept in a computer database only accessible to the PI and Senior Research Coordinator. After the randomized trial data are analyzed, the list will be destroyed. If any publications result from this phase, no identifying information about an individual will be included.

c. Potential Risks – Phase II

This research does not pose any clear physical risk to participants, although any research may have unforeseen risks. Confidentiality is protected according to our institutional standards. Access to lists linking identifying information to participant numbers is restricted. Women will be asked to focus on sensitive material, i.e. sexual problems that women experience after cancer treatment. Some participants may find this embarrassing or emotionally distressing, but given that they will be informed in advance of the subject nature of the project, women who do not want to deal with sexual issues are unlikely to participate. Any psychoeducational intervention may cause some emotional distress, and this may not be recognized immediately, particularly for women in the self-help condition. However, we have never had an adverse event in our similar intervention studies. An alternative would be to seek professional sexual counseling or medical care for sexual dysfunction rather than participate in the randomized trial.

2. Adequacy of Protection against Risks- Phase I

a. Recruitment and Informed Consent – Phase II

Participants in Phase II will be recruited mainly through letters sent to people in the tumor registry who have agreed to be contacted for future research studies, flyers placed in outpatient areas of UTMDACC, public service announcements, or through our volunteer Anderson network. Women from the community may also participate, and special efforts to ensure participation of minority and underserved women may include using our community contacts to inform cancer survivors of desired age or ethnicity about the study. Women who are interested in the study after receiving letters, flyers, or information from their oncology physician, will contact the study research coordinator (Lorna Mangus). She will perform a telephone screening of eligibility, including screening for sexual dysfunction by administration of the 19-item FSFI. She will also review the informed consent form. Women who are eligible will be mailed a written informed consent form, approved by our IRB and conforming to our institutional standards. When the completed packet and signed informed consent are returned, women will be minimized to one of the two groups and given a username, password, and the URL of the *Tendrils* website with instructions to complete the baseline questionnaires online. Women will need to have signed the informed consent form before they will be able to access the website or participate in counseling sessions. The informed consent form will include a discussion of confidentiality protections for the website, the questionnaires, and audiotapes of some counseling sessions to assess quality control of the intervention. Participants will be have paid parking or transportation to the medical center.

b. Protection against Risk – Phase II

We have never yet had an adverse event in one of our sexual counseling intervention studies, but any psychoeducational intervention can trigger emotional distress in some participants. We use the BSI-18 to track emotional distress in participants. We score the BSI-18 within 48 hours of receiving a questionnaire packet, and if a woman meets “caseness” criteria, the Senior Research Coordinator or counselor will contact the participant by phone to see if she has adequate social support and mental health services. Dr. Schover will be consulted as well. If a participant needs mental health services, we will give her an appropriate referral or intervene as needed if we feel there is any imminent danger of her harming herself or others. These procedures will be described in the informed consent process. We also will inform all participants that if they are distressed they can page the counselor for the study. This master’s-level counselors will be supervised by Dr. Schover, who is a clinical psychologist licensed in Texas. The counselor will carry a pager in case of any mental health emergencies. The counselor can then in turn

contact Dr. Schover or another licensed faculty member in our department. We have an on-call plan in the new Behavioral Research Treatment Center. We can talk with the participant on the phone or if necessary, meet with her in person to ensure that she has a referral for appropriate mental or medical health care. In addition, Dr. Schover will have supervision sessions with the counselor at least once every 2 weeks or weekly during normal participant volume. The randomized trial provides information and help that goes beyond usual care, but women always have the option of not participating in the research and instead, seeking mental health or medical care for their sexual problems from a professional. The protections of confidentiality in our database are standard for our research and conform to both institutional and HIPAA regulations. Both the *Tendrils* material and the counselor will promote seeking medical care to evaluate any potential signs of cancer recurrence or other disease, for example vaginal bleeding or nipple discharge. When medical interventions, such as hormonal replacement or vaginal dilators are discussed, potential health risks will be appropriately highlighted.

3. Potential Benefits of the Proposed Research to the Subjects and Others – Phase II

Participants in Phase II may learn some helpful information or improve their sexual function or satisfaction, but also may not benefit at all from participating. However, this is a low risk study, and the potential benefits to participants and future patients clearly outweigh the minor risks.

4. Importance of the Knowledge to be Gained – Phase II

This research is important because an estimated 3 million women cancer survivors in the United States suffer in the long-term from sexual dysfunction related to their cancer treatment. There are currently few good patient education materials available, and access to mental health or medical treatments for these problems is also limited by lack of trained professionals, stigmatization of seeking help for a sexual problem, and limited insurance coverage. Creating a multimedia intervention for these problems will give many more women access to needed information, and should empower women to resolve sexual problems by using self-help strategies or seeking appropriate professional care. Phase II will help us assess the efficacy of the intervention both used as a self-help program and in the context of brief professional counseling.

5. Data and Safety Monitoring Plan – Phase II

This protocol would not be initiated until fully approved by the UTMDACC IRB. Our institution has a standard Data and Safety Monitoring Plan, including an institutional Data Monitoring Committee. For behavioral protocols such as this one that are relatively low in risk, the IRB usually does not require a formal Data Monitoring Committee interim evaluation or stopping rule. Since the planned randomized trial conforms more to the description of an NIH Phase II trial than a Phase III trial, and will only be in progress for a year, an early stopping rule is not relevant. Even if interim analyses at 6 months suggested that the counseling group was improving more in sexual function or satisfaction than the self-help group, it is important to track sexual function for at least 6 months to see if gains are maintained before marking a decision that one treatment group is superior. The PI will monitor the safe conduct of the randomized trial, submitting a yearly progress report to the IRB. Expected adverse events would include a mild increase in emotional distress because of focusing on an unpleasant consequence of cancer treatment, or because trying to alleviate the sexual problem might cause relationship distress. Such expected events do not have to be reported as serious adverse events. Any unexpected, severe adverse event, such as a psychiatric hospitalization or suicide attempt by a participant occurring within 30 days following the last participation date will be formally reported to the IRB and to the National Cancer Institute within 5 working days of knowledge of the event. Any death with possible, probably or definite attribution to participating in this study would have a written report submitted to the IRB within 24 hours of knowledge of the event.

INCLUSION OF WOMEN AND MINORITIES

A targeted and planned enrollment table is provided below. Since this study focuses exclusively on female sexual dysfunction, male participants will not be included. Given the ethnic composition of Houston, we hope to recruit slightly higher percentages of Spanish-surnamed and African-American women than make up our tumor registry, i.e. 15% of subjects in each of these two groups, and 5% Asian-American women, so that Anglo women make up 65% of our sample. It is important to have a diverse sample because we want to ensure that our intervention is culturally sensitive and useful to a broad spectrum of cancer survivors. Realistically, we may not have enough minority participants to allow us to compare efficacy of *Tendrils* for Anglo women vs. any other ethnic group, however. That would require a larger, Phase III randomized trial. We have good relationships with the African-American survivor community in Houston because of our *SPIRIT* project, and have been able to recruit by giving talks and having flyers at churches with cancer ministries and other community organizations. We also will get IRB approval to recruit participants at the oncology clinic run by UTMDACC faculty at our county hospital, which has a more underserved population. We expect that cervical cancer patients will also be a more diverse group than breast cancer patients. We also have worked with our Center for Research in Minority Health in recruitment. They have community liaisons with the Hispanic and Asian communities. It is often more difficult to recruit minority women for sexuality research, even using the typical strategies for minority recruitment, because of cultural norms about the privacy of sexuality, however.

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Tendrils: A Multimedia Intervention for Women's Sexual Dysfunction after Cancer

Total Planned Enrollment: 240

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	36	0	36
Not Hispanic or Latino	204	0	204
Ethnic Category: Total of All Subjects *		0	240
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	12	0	12
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	36	0	36
White	192	0	192
Racial Categories: Total of All Subjects *	240	0	240

* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

INCLUSION OF CHILDREN

Since the study involves a focus on sexual behavior and function, children under the age of 18 will not be included. However, women aged 18 to 21 will be included with informed consent. At our institution, parental consent is only required for participants under age 18.

DATA AND SAFETY MONITORING PLAN

The Data and Safety Monitoring Plan for Phase II was described in Section 6. If the application is funded, we will create a formal plan as part of the IRB approval process.

TENDRILS MARKETING PLAN

A. Value of the STTR Project, Expected Outcomes, and Impact

Sexual dysfunction is the most common long-term consequence of cancer treatment, affecting half of survivors of breast and gynecological cancer and many women treated for other cancers, e.g. at least 3 million women in the United States. In contrast to other sources of psychosocial distress, sexual dysfunction persists long after cancer treatment and is usually pervasive, diminishing sexual desire and affecting intimacy. Although the causes of these problems are known, and brief counseling is often effective at resolving them, few women have access to such information or services. Thus the potential for commercial sales of an affordable, effective, multimedia program for sexual rehabilitation is very large.

We propose to develop and evaluate a multimedia intervention program for women with cancer-related sexual dysfunction. *Tendrils: A Sexual Renewal Program for Women Surviving* will be designed: 1) to answer women's questions about cancer-related sexual dysfunction; 2) to offer self-help strategies to overcome problems; 3) to encourage women to seek medical help when appropriate; and 4) possibly to serve as the nucleus of a brief, professional counseling program, along with a therapist manual. Its content will be comprehensive and medically accurate, using tasteful animations rather than live actors to illustrate any direct genital anatomy or sexual options. Situations that should trigger consultation with a physician will be highlighted. Despite the many different cancer sites and treatments for women, sexual dysfunction after cancer tends to divide into several common patterns, particularly loss of desire, genital pain, and concerns about being attractive and lovable to a partner. *Tendrils* will be relevant to a broad spectrum of women, from newly diagnosed to long-term survivors, with sections for women with specific cancer sites or with advanced disease. Designed to appeal to women of differing ethnicity, literacy level, and sexual orientation, *Tendrils* will present material on a variety of religious and cultural attitudes about female sexuality. A section for partners will also be included. The software used to construct it will allow women to interact with the material in a variety of formats, including printed out pages, computer animations, and digital video or audio files that can be used on a computer or downloaded to a personal digital assistant or media player. Video vignettes portrayed by actors will illustrate problems and solutions. Five cancer survivors of varying age, ethnicity, and sexual orientation will host the program, sharing their experiences. Their stories will be viewable as units, or in shorter segments linked to relevant content. Although the plan for Phase I and II does not include translation to Spanish, mainly because of added expense to the budget, translation will be accomplished as part of the commercialization phase.

Tendrils will fill an important need among cancer survivors because it addresses a highly prevalent problem for women that is currently only superficially reviewed in patient education resources. No evidence-based treatment programs specifically focus on women's sexual problems after cancer. By creating a multimedia tool that can be used either on a self-help basis or as part of a brief counseling program with a counselor manual aimed at oncology nurses or social workers with some basic counseling skills, our product potentially overcomes the following barriers to successful sexual rehabilitation for women after cancer:

- Existing patient education materials only explore basic issues and are formatted for well-educated women who read brochures or self-help books. A multimedia intervention can reach lower-literacy women by using voice-overs and videos, and by appearing more appealing than a book or brochure. The inclusion of vignettes and survivor stories on video also models how to cope with sexual problems and provides a sense of support for women who may not be comfortable discussing sexuality in a support group or with friends or family.
- Few health care professionals are trained to deliver sexual counseling for cancer-related dysfunction. Yet, there are many oncology social workers and nurses with the basic skills to be able to deliver sexual counseling if they have a curriculum. The counselor manual plus *Tendrils* itself would encourage such counseling.
- Seeking help from a mental health professional for a sexual problem is still stigmatized, even more so for women from minority groups. Yet, women might be very eager to try an affordable self-help option.
- Insurance coverage is poor for traditional sexual counseling from a mental health professional. Again, self-help applications are one way to transcend this barrier, and another is to have more

trained oncology nurses and social workers in major cancer centers or private practice oncology clinics who might offer supportive sexual counseling free of charge as part of psychosocial services. Women who are older, have less education, or are less comfortable with computers might particularly benefit from having a counselor guide them through the *Tendrils* program. Our research in Phase II will try to identify whether age or education makes a difference in the efficacy of *Tendrils* in improving sexual function in a self-help vs. counseling mode.

• Women often are unsuccessful in finding a medical specialist who can treat physical causes of sexual dysfunction. *Tendrils* will educate women on the types of medical options that may be helpful, how to find skilled practitioners, and how to be assertive in seeking quality care.

In its 2003-2004 report, Living Beyond Cancer, the President's Cancer Panel made this recommendation: "Health care providers should not assume that older cancer survivors and their partners are uninterested in sexuality and intimacy. Survivors should be asked directly if they have concerns or are experiencing problems in this area and should receive appropriate referrals to address such issues." However, women of all ages treated in the United States and other developed countries still tend to receive little or no information on cancer-related sexual dysfunction. The information in this paragraph is presented in the body of the grant proposal with references, but is worth summarizing again here to understand the magnitude of the resource gap for women who have cancer-related sexual dysfunction. A survey of the patient education departments of comprehensive cancer centers in 2002 revealed that only 14% offered counseling on sexuality. In a group of 166 well-educated women diagnosed in the Northeast with premenopausal breast cancer, only 68% recalled being informed about premature menopause by one of their physicians, let alone having a discussion directly about sexual function. Premature ovarian failure is a major health consequence affecting the majority of women who have adjuvant chemotherapy for breast cancer and are aged 35-50. It increases long-term risks of osteoporosis and cardiac disease, and brings unpleasant symptoms of hot flashes and vaginal dryness. A major reason that health care professionals give for failing to bring up the topic of sexuality is lack of knowledge on how to help the patient directly, as well as a dearth of resources for patient education and referral. In general, only about 20% of women in the United States, regardless of health history, seek professional help when they have a sexual problem. When they do, they often consult their gynecologist and in a recent internet survey, only 14% ended up with a diagnosis or treatment plan. About half felt the physician did not want to hear about their problem.

Currently, Dr. Schover, the PI of this project, has written the majority of patient education materials used nationally on female sexuality and cancer, including the sections of the Lance Armstrong Foundation's survivorship LiveStrong information on male and female sexuality and a booklet on ovarian cancer and sexuality for the National Ovarian Cancer Coalition.. In 1988, she wrote two extensive booklets on sexuality and cancer for the American Cancer Society (ACS) for men and women. They have been updated every several years since, remaining the most popular patient education materials ever produced by that organization, with hundreds of thousands of copies distributed. A few revisions have been made that she does not endorse, such as advocating the use of androgen replacement for women with low desire, but the text remains about 90% faithful to the original. It is available free of charge on the ACS website at http://www.cancer.org/docroot/MIT/MIT_7_1x_SexualityforWomenandTheirPartners.asp. In 1997, Schover published a self-help book, *Sexuality and Fertility after Cancer* with John Wiley & Sons. A trade paperback, it sold approximately 3,800 copies and is currently being remaindered. Despite excellent reviews, it was not well-publicized. It provided more detail in all respects than the ACS booklets and also included chapters on fertility after cancer. However, as we discuss in the main body of the grant, self-help books and pamphlets have limited impact, because they are primarily read by college-educated women over age 55. Educated, younger women in their 30s to 50s tend to be the most active information-seekers among cancer patients, and they are increasing turning to the internet and online support groups. Information about sexuality and body image accounts for about 4% of information needs among newly diagnosed cancer patients, but this figure, although important in itself, is a major underestimate, since sexual function becomes a much more salient problem in the longer-term survivorship period.

Obviously one major innovation in *Tendrils* is making full use of robust media that can be viewed in a variety of formats. Another innovation is using feedback from expert professionals, cancer advocates, and focus groups of survivors to ensure that *Tendrils* is easy to use, relevant, and acceptable, given the sensitivity of the topic. We have chosen, in Phase II to create a somewhat ambitious plan to test the efficacy

of *Tendrils* in a self-help mode vs. in counseling mode. We want to create a truly evidence-based treatment, and not just an educational application. Once we have a revised, complete prototype of *Tendrils* ready to be accessed on a website, we will recruit 240 women, 1-5-year survivors of breast or gynecological cancer, free of disease, and off active cancer treatment. Women will be randomized to two treatment groups, balancing cancer site, age group, menopausal status, and educational level. The self-help group will access *Tendrils* on a website for a 12-week period. The counseling group will access the website for 12 weeks and attend 3 sessions with a trained counselor. Women will complete online questionnaires at baseline, after treatment, and at 3- and 6-month follow-up. Time spent using the website will be recorded and women will estimate time spent weekly reading printouts, using downloaded files, or doing behavioral homework. Our primary hypothesis is that *Tendrils* will produce significant improvements in sexual function and satisfaction whether used on a self-help basis or with brief counseling, but that the counseling group will improve significantly more than the self-help group. Secondary hypotheses are that counseling will add more benefit for less educated women and older women. Time spent using *Tendrils* will be examined as a potential mediator of success. Trial outcome will be used to target marketing of *Tendrils* optimally, in accordance with the principles of evidence-based medicine.

B. Company.

AXIS Healthcare Communications LLC provides a full spectrum of services to support the lifecycle of pharmaceuticals, and medical devices, from Phase II trials to patent expiration, at global, regional, and local levels. Our seven US-wide companies specialize in providing strategic consulting, analysis and planning, medical communications, medical education, sales training, and healthcare advertising and promotion.

AXIS was founded as ApotheCom Associates LLC in 1999. The business developed partnerships with major pharmaceutical companies and has grown in this manner from having 4 to 260 employees. In 2002, AXIS was formed as a holding company to centralize accounting, IT, human resources, creative, and digital services, in order to increase business efficiency. AXIS has annual sales around $65M, mostly from fee for strategic services and execution of tactics. AXIS company locations are strategically positioned near clients in order to serve them cost-effectively. AXIS has one of the highest proportions of health professionals as employees in our industry including about 45% MDs, PhDs, and PharmDs. Full time staff at AXIS has hundreds of combined years of experience in launching health products. We consider all aspects of the product science, marketplace, and competition. We have active relationships with major research leaders, clinicians, and health and professional organizations in most geographic areas throughout the United States.

Most of our business is generated from partnerships with pharmaceutical companies. As these companies produce more complex products to cure health problems, the need to educate health care providers and patients will continue to grow. Because people with cancer are living longer and longer every year due to improved treatments, survivorship is presenting a new set of physical and mental health problems. We believe when we approach pharmaceutical companies about supporting the distribution and licensing of our grant-funded product that they will welcome this opportunity. Because all of the content in the program was fully developed without pharmaceutical company involvement, there is not an agenda to support a specific treatment. Thus our healthcare professional audiences will not be concerned with the quality of the content, and can embrace the program. We feel pharmaceutical companies will want to play a part in helping us reach healthcare professionals with our program, because it is consistent with their current business practices of promoting quality of life for cancer survivors and providing educational materials for health care professionals.

AXIS stays current with regulatory guidelines and regularly updates its best practices through formal direction given throughout the company. Our central office runs AXIS University, an educational program that offers relevant business training to all AXIS employees.

AXIS has embraced the opportunity to work with U. T. M. D. Anderson Cancer Center on the National Cancer Institute grant R44 CA-88088. Working on the project was a great fit for our in-house creative and multimedia teams. Our digital team built the entire robust prototype in-house including interface design, navigation strategy and elements, creative branding, and programming. We are currently updating the final prototype to the marketable product by incorporating feedback from Dr. Schover's clinical research using the intervention at UTMDACC. We have a product director for the marketing phase with years of

experience taking products to market, and who incidentally is also a cancer survivor. We are beginning to form an advisory board of experts with experience in oncology clinical practice and business who will help us optimally position the product in the marketplace.

The current project also allows us to benefit from the expertise of Cancervive, Inc., a nonprofit corporation that has created over 20 videotapes, games, books, and packaged products to improve the quality of life of cancer survivors. They have won a number of awards for their products, and have had a series of partnerships with pharmaceutical corporations in funding and distributing them. We are looking forward to learning from their knowledge of this particular audience as well as their experience in partnering with corporations.

C. Market, Customer, and Competition

In terms of direct marketing to cancer patients and survivors, we use references in the body of the grant proposal to demonstrate that at least 3 million women in the United States today are affected by cancer-related sexual dysfunction, with a new group of at least 400,000 women diagnosed yearly who can expect to encounter these problems. Most of these women are over age 50, but *Tendrils* will have information for the entire range of women, from survivors of childhood cancer to women of mature years. It will also include information relevant to newly diagnosed women, who may still be making treatment decisions, to long-term survivors, and to women with advanced disease who want to stay intimate with their beloved partners. We hope to appeal to women of a broader educational range than those who read self-help books, though we acknowledge that women who are functionally illiterate or do not understand English or Spanish (since we plan to translate *Tendrils* and use consultants to create a culturally-sensitive Spanish version in the marketing phase) may not benefit. Even if only the 20% of women who seek professional help were interested in Tendrils, the target market would include over 600,000 women. However, many women who are reluctant to ask a physician about a sexual problem may be enthusiastic about accessing a self-help resource.

Reaching this direct market is not difficult. The Health Information National Trends Survey (HINTS), conducted by the National Cancer Institute in 2000-2003 gives some insight into cancer survivors' search for cancer-related information, (although with rapidly increasing use of the internet, some of the estimates of internet use may already be dated). In a presentation at the HINTS Data Users Conference, in January, 2005, by Whitney Randolph Steele, Ph.D., M.P.H., NCI, titled, Information Seeking and Information Needs of Short- and Long-Term Cancer Survivors: Comparison of Strategies across the Continuum, responses of 720 cancer survivors were compared with the much larger sample of respondents without a history of cancer. Cancer survivors were more likely to be women, and were older with 41% age 65 or more. They were significantly more likely to have searched for information about cancer recently (70% vs. 45% of the general population), and more likely to be frustrated and dissatisfied with the information they found. In terms of sources of information, 36% used the internet, 20% asked a health care provider, 18% used books or written brochures, and 12% looked in magazines or newspapers. *Tendrils* could easily be marketed through such avenues, including advertising on websites of trusted advocacy organizations or on search engine websites, marketing through the patient education libraries of cancer centers and hospitals, and public relations articles or paid advertising in magazines geared to cancer survivors.

Cancer is the most researched health topic on the internet. Beast cancer survivors, in particular, have become a highly organized group with many organizations and websites. The National Ovarian Cancer Coalition is also an umbrella group for several smaller, national organizations for this most common of the gynecological cancers. We could seek endorsements of *Tendrils* by some advocacy groups, and potentially have links to a marketing site from their websites. If they sell their mailing lists, direct mail advertising would be another option. We could also purchase advertising on search engine pages for topics such as breast cancer, ovarian cancer, cervical cancer, etc.

Several magazines are geared specifically for cancer patients and survivors and would be excellent venues for paid advertising. Mamm, founded in 1997, publishes 10 issues a year specifically about breast and reproductive system cancers. Its current circulation was not mentioned on the internet, but in 1999 it was 91,000 with a goal of 250,000. CURE (Cancer Updates, Research & Education) is published quarterly and distributed without charge. According to their website they reach 425,000 cancer patients, 52% with

more than a high school education. They are preparing to publish a sister magazine, HEAL, that will be geared to cancer survivors, who are finished with treatment. In England, a magazine called I CAN is similar. Advertising in such publications would be one way to publicize *Tendrils*, as would having a dedicated website for marketing.

Oncology healthcare professionals who focus on quality of life issues are another target audience, not only for the counseling package of *Tendrils* plus counselor manual, but also in terms of informing patients of this resource. The Oncology Nursing Society (ONS) has over 30,000 members and holds an annual meeting. The Association of Oncology Social Workers (AOSW) has over 900 members. They publish a quarterly newsletter and hold an annual conference. The American Psychosocial Oncology Society (APOS) is a newer, multidisciplinary organization for mental health professionals who specialize in working with cancer patients and survivors. It has at least 300 members and holds an annual meeting and has a website that presents educational materials and a mental health referral service. We could potentially present a research paper about evaluating *Tendrils* at such conferences or submit a workshop on training nurses or social workers to use it as part of a counseling program. We also could advertise to the mail or email lists of such societies.

Another possibility is that *Tendrils* will become part of a line of evidence-based, multimedia patient education and intervention tools marketed under the UT M. D. Anderson Cancer Center (UTMDACC) "brand." As one of the two premier comprehensive cancer centers in the United States, UTMDACC has its own marketing and public relations departments. Recently, Dr. Schover has been working with them to develop a proposal to present to the UTMDACC administration to create a Center for Reproductive Health that would treat sexual dysfunction and also offer fertility preservation and infertility treatment to women. One aspect of the center would be its unique international profile as a place for on-site professional specialist training. The center could also develop and market a "line" of patient education materials for direct marketing to cancer patients and survivors. The Mayo Clinic has probably been more successful than any other health care organization at marketing books and other patient education materials under its name. This year they published *The Mayo Clinic Guide to Women's Cancers*, focusing on breast and gynecological malignancies. Although this book is widely available, it only devotes 20 pages to quality-of-life survivorship issues, and 6 pages to sexuality. The American Cancer Society has in-house book publishing, but we are not aware of any plans to produce a book on sexuality and cancer. In fact, Dr. Schover had spoken to their director of publications several years ago about trying to reclaim the copyright for *Sexuality and Fertility after Cancer* in order to update and expand it for publication with them, but John Wiley & Sons were unwilling to give up the rights at that time.

In terms of other books, Dr. Schover's book will now be out of print. Deborah Hobler Kahane's 1995 book, No Less a Woman, recounts her personal experience with breast cancer, but is not designed to be a comprehensive resource on sexual rehabilitation. New books on female sexuality in general are published periodically, but do not contain the specialized information needed by cancer survivors who have problems directly related to their treatment. Such books often are written by authors who are unqualified, or promote bogus concepts such as the superiority of "G spot" orgasms, the idea that removal of the cervix during hysterectomy damages orgasmic capacity (contradicted by several large, randomized trials published in prestigious journals), or the idea that most postmenopausal women lose desire for sex and need to take testosterone (a particularly dangerous piece of misinformation given clearly increased risk of breast cancer in women who use these hormones.

Surprisingly, a search of websites such as Amazon.com, borders.com, or Google did not turn up any multimedia educational applications even on general female sexuality. For women who have "vaginismus," a phobia about vaginal penetration that prevents comfortable sexual intercourse, a book and videotape are marketed on the internet as a package, along with a set of vaginal dilators in graduated sizes. This type of treatment can be adapted for women who have pain with intercourse after cancer treatment, but the goals and methods will be somewhat different. Thus *Tendrils* faces little or no direct competition and has a potentially very large market. We are not aware of anyone working on a similar project.

If UTMDACC does not want to venture into a strategic partnership to market *Tendrils* it may be possible to create such a partnership with the Lance Armstrong Foundation's LiveStrong project, or with the American Cancer Society's publications department. A pharmaceutical company may also be interested in licensing rights, since this would be a very attractive, high-profile product to give out at national conferences or to distribute to cancer centers and oncology clinics as part of marketing of new chemotherapy drugs or

hormonal therapies. The counseling package with *Tendrils* plus a counselor manual might be particularly attractive to companies who focus marketing efforts on oncology nurses. Not only does AXIS have extensive connections with pharmaceutical corporations with oncology products, but the Cancervive team has also been quite successful in securing such funding.

D. Intellectual Property (IP) Protection.

AXIS communicates regularly with its legal advisors for protecting intellectual property. We have a long term relationship with a law firm in nearby New York City, NY. This firm specializes in our business of healthcare communications and knows our marketplace and competition well. We will work with this firm to evaluate and obtain the most appropriate level of intellectual property protection for this product, as we do with all of our products. Because of our ongoing working relationship with this firm, we can secure property with high efficiency and at a reasonable cost.

In addition to protecting our own property, AXIS respects the intellectual property of others. AXIS has purchased a U.S. annual copyright license through the Copyright Clearance Center (CCC). The license has been purchased under the AXIS Healthcare Communications LLC name and covers all AXIS companies.

The license provides rights for any AXIS employee to use and share information internally throughout the year. This license provides reuse of content from the CCC massive catalog of the most sought-after titles from news and trades, business, society, finance and scientific, technical and medical publishers. In addition, the license eliminates the burden of tracking and managing content use throughout the organization.

E. Finance Plan

The total number of female cancer survivors in the United States (US) in 2004 was estimated to be about 5.6 million. Pelvic and breast cancers comprise over two-thirds of the disease sites for these women.1 In 2005 another 397,220 women were expected to receive new diagnoses of pelvic or breast tumors.2 Thus a conservative estimate is that 3 million female cancer survivors in the US suffer from sexual dysfunction. Even if only 20% were interested in *Tendrils*, corresponding to the 20% who currently seek professional help, we would have a potential market of over 600,000 women. In considering our finance plan, we begin with these numbers.

AXIS companies combined generate $10 million in revenue annually in the oncology marketplace, working primarily with pharmaceutical companies. This represents about 15% of our total revenue. Because of our ongoing business relationships with our clients, we are able to introduce products very early in their development, in order to create excitement and strategically plan numerous potential positions for the product in the market. We plan and budget with our clients on average about 6 months ahead for the upcoming year.

The costs to introduce the product to our existing clients is negligible, because we are already planning to invest this same time presenting ideas, strategies, and tactics to these corporations. Because this product gives us the opportunity to offer a different, novel means for our clients to contribute to improving health care, it will be embraced by our business development teams.

F. Production and Marketing Plan

The costs to actually produce *Tendrils* do not represent an obstacle, since our company routinely produces CD-ROMs and web sites, the two most likely formats in which we would market this application. Production costs are actually quite low compared to the costs of creating the application, with content development, computer programming, and creative artwork, animations, and videos.

AXIS uses a software package, Marketing Plan Pro Premier, to develop product marketing plans. The software ensures that all details are covered and logically placed, supporting the marketing process

from initial development of a product through the implementation phase. We have used the software to successfully position several products, services, and business partnerships.

For *Tendrils*, we will begin by developing a positioning statement or objective that serves to define the mission for the product. We then define our customer, and create a customer-centered set of offerings that are covered by the product. One key to product marketing is focusing on the benefits the product offers the customer. Next we'll create similar descriptions of competitor products, and begin to formulate specific opportunities in the marketplace for our product.

In examining our market, we will take a systematic approach, considering the geographic, demographic, psychographic, and behavioral components. For example, offering different product options optimized to age and likelihood of having broadband Internet access may increase the product's appeal and to certain survivor groups. Targeting younger audiences with program content playable on their iPods would be a good fit, as would offering CDs to people with limited Internet access. Market trends and growth / decline are routinely examined. We adjust our approach regularly throughout the execution of a product plan.

We will optimize product-to-market fit and prioritize our efforts by creating a “SWOT” analysis: examing the Strengths, weaknesses, Opportunities, and Threats surrounding our product Although currently there are no competing products, if some emerge during the project, we will repeat the SWOT analysis based on their characteristics. Ultimately we will be able to categorize our marketing plan for *Tendrils* as ideal, speculative, mature, or troubled. We can then act appropriately to address the challenges we identify.

We will define hard numbers for the reasonable costs of marketing and production to ensure we have appropriate financial resources for each step. We will create a diagram showing the logical connection between marketing programs we develop for each target audience and each marketing strategy, providing a clear and logical rhythm to our marketing process that will motivate team members and ensure continued corporate support of our marketing efforts.

We are completing the final revisions to our *Banking on Fatherhood After Cancer* (BOFAC) program, sponsored by a grant from the National Cancer Institute, and have started its marketing plan. By the time we are considering *Tendrils* for market, we will have a board of advisors in place from crucial segments of the oncology healthcare industry. We should have a smooth transition in adding this second product to our portfolio. We anticipate that the high quality of the BOFAC program will create excitement in our marketing team and our customers, who will look to us for more high quality, innovative products. *Tendrils* will thus be a perfect fit in this product line.

We will create a reasonable, but aggressive sales forecast and a detailed expense budget. We will develop an approximate time schedule for anticipated financial returns on our marketing investment. Revenues will be distributed according to the agreement we reach in our STTR consortium. Some of the AXIS revenues will be dedicated to further marketing efforts and product development. Because *Tendrils* offers the greatest value if its content is most current, we will rely on our sales forecast to determine funding for content updates. Our prospects and customers expect periodic alerts about program updates. Because all AXIS companies are required to submit sales forecasts and budgets for their departments at regularly scheduled intervals, we are simply following an existing process.

AXIS has accounting and financial systems in place today that we can use to track marketing implementation for *Tendrils*. Our implementation milestones will be used to create the sales forecast, resulting in a sales plan. We will monitor all sales by managing data using one system that offers easy input (automatic and manual) and tracking of all point-of-sale transactions. We will know how many CDs or Web subscriptions or video Podcasts we need to sell in order to break even with our marketing, content updates, and other maintenance costs. In addition to experience in marketing health products, publication planning is one of our core areas of expertise and experience. We currently help our pharmaceutical clients strategically publish clinical trial data generated by their products. In order to do this well, we have gained a significant network of contacts in the health publishing arena, including members of editorial boards and medical societies. We plan to leverage these contacts to create novel ways to disseminate the *Tendrils* program, and to get input on distribution channels that will be most fruitful for our efforts.

Tracking Sales and Purchaser Demographics. The Cancer Communications SBIR/STTR program mandates that the marketing plan for this proposal include a plan to track demographic characteristics of purchasers. If *Tendrils* is marketed on a CD-Rom, or as downloadable software, our plan

would be to require registration online to activate the product. Users would be asked to complete multiple-choice questions about gender, cancer site, age, education, and ethnicity. The registration would actually tailor the product by adding highlights to sections particularly likely to be useful to the purchaser, based on this information. The information would be sent to the production team, but without any identifiers, such as name or city of residence. This confidentiality protection would be explained on the website. Another option would be to make the *Tendrils* product usable without registration, but to give added value to users who register: i.e. 1) customized navigation indicators and 2) access to a *Tendrils* news updates website that would have a monthly front page featuring newsworthy research findings or clinical tips relevant to women with cancer-related sexual dysfunction.

G. Revenue Stream

We are in an advantageous position because both Axis and UT M. D. Anderson Cancer Center have stable revenues and do not depend on the profits from one application for survival. In fact, an application like *Tendrils* helps to generate revenue for both partners. Axis Healthcare Communications generates most of its revenue by developing marketing and educational materials, typically as part of the process of helping pharmaceutical companies prepare drug and device products during the pre-launch, post-launch, and primary marketing stages of their lifecycles in various markets. A major source of revenue from our clients compensates us to produce educational materials for physicians and patients. Our corporate clients seek to increase awareness of health issues, ultimately contributing to the identification of new patients and improving the treatment of their illnesses. In the oncology marketplace, we develop educational materials for physicians and patients on cancer screening and early identification, diagnosis and optimal treatment plans, and chronic care needs of survivors, putting us in a perfect position to market the *Tendrils* program.

In addition to revenues from direct sales of the Tendrils program, it becomes a showpiece for our company. We will demonstrate *Tendrils* as part of our product showcase in pitches for new business to demonstrate our creative capabilities. Creating a high-quality, evidenced-base application like *Tendrils* increases our status in the industry, particularly given the prestige of being funded by the National Cancer Institute and partnering with the University of Texas M. D. Anderson Cancer Center. We have already experienced this advantage in business development settings when we have demonstrated our current NCI project, *Banking on Fatherhood After Cancer*.

For the UT M. D. Anderson Cancer Center, *Tendrils* has potential public relations value. Having an application to improve quality of life for cancer survivors come out of the nation's premier cancer center demonstrates concern for patients. UT M. D. Anderson's marketing seeks both national and international patients who can come to Houston to get not only the best medical care, but treatment in a caring, humanistic environment.

In summary, we believe that *Tendrils* is eminently salable, and will benefit from the marking expertise, resources, and network of Axis Healthcare Communications, LLC, with negligible financial risk to any of the partners in this consortium.

Long-term Objectives Aims: Sexual dysfunction is the most common long-term consequence of cancer treatment, affecting half of survivors of breast and gynecological cancer and many women treated for other cancers. Yet, few women get the help they need for sexual problems. **Our primary objective is to develop and evaluate a multimedia intervention program for women with cancer-related sexual dysfunction.** *Tendrils: A Sexual Renewal Program for Women Surviving Cancer* will: 1) explain the causes of cancer-related sexual dysfunction; 2) offer self-help strategies to prevent or overcome problems; 3) advise women on seeking appropriate medical help; and 4) possibly serve as the core of a counseling program, along with a therapist manual. *Tendrils* is aimed at a wide audience, from newly diagnosed to long-term survivors, across cancer sites. Material will be presented with sensitivity to religious and cultural attitudes about sexuality. Animations will illustrate anatomy and physiology. The software will let women use *Tendrils* in a variety of formats: over the internet, on a CD-Rom, printed out, or as downloaded digital video or audio on a handheld computer or media player. Video vignettes will illustrate problems and strategies. Four female cancer survivors will host the program, sharing their experiences.

Research Design and Methods: In Phase I, a prototype of *Tendrils* will be created including text, sample animation concepts, and scripts of vignettes. Ten expert professionals and cancer advocates will view the prototype on a website, as will 3 focus groups of female survivors. Feasibility will be shown if at least 75% rate *Tendrils* as meeting criteria for ease of use, comprehensibility, and relevance on an evaluation form. In Phase II, a revised, complete prototype of *Tendrils* will be created. We will recruit 240 women, 1-5-year survivors of breast or gynecological cancer, free of disease, and off active cancer treatment. Women will be randomized to two treatment groups, balancing cancer site, age group, menopausal status, and educational level. The self-help group will access *Tendrils* on a website for a 12-week period. The counseling group will access the website for 12 weeks and attend 3 sessions with a trained counselor. Women will complete online questionnaires at baseline, after treatment, and at 3- and 6-month follow-up. Time spent using the website will be recorded and women will estimate time spent weekly reading printouts, using downloaded files, or doing behavioral homework. **Our primary hypothesis is that *Tendrils* will produce significant improvements in sexual function and satisfaction whether used on a self-help basis or with brief counseling, but that the counseling group will improve significantly more than the self-help group. Secondary hypotheses are that counseling will add more benefit for less educated women and older women. Time spent using *Tendrils* will be examined as a potential mediator of success.** Trial outcome will be used to target marketing of *Tendrils* optimally.

Project Relevance:
Sexual problems related to cancer treatment affect approximately half of female survivors of breast or pelvic cancer and a smaller, but significant, proportion of women treated for other malignancies, e.g. at least 3 million women in the United States. In contrast to other sources of psychosocial distress, sexual dysfunction persists long after cancer treatment and is usually pervasive, diminishing sexual desire and affecting intimacy. Although the causes of these problems are known, and brief counseling is often effective at resolving them, few women have access to such information or services.

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